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GRANT NUMBER: DAMD17-94-J-4507

TITLE: Managing Menopausal Symptoms in Breast Cancer Survivors

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REPORT DATE: October 1999

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5102

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1999	Final (23 Sep 95 - 22 Sep 99)

4. TITLE AND SUBTITLE
Managing Menopausal Symptoms in Breast Cancer Survivors

5. FUNDING NUMBERS
DAMD17-94-J-4507

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release
distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

Menopausal symptoms commonly occur in breast cancer survivors. In this research program we evaluated the efficacy of a comprehensive menopausal assessment (CMA) and intervention program for management of menopausal symptoms (hot flashes, vaginal dryness, urinary incontinence) in this target population. Primary outcomes were symptom relief and energy/vitality, with sexual functioning as a secondary outcome. We recruited 72 moderately symptomatic breast cancer survivors who were randomly assigned to either usual care or the CMA intervention. All breast cancer survivors completed standardized assessment measures of symptoms and quality of life before randomization and at the end of the four-month follow-up period. Assessments of hormonal status and vaginal health were also part of the study. Results from the study show that the CMA program was effective in significantly reducing menopausal symptoms (using non-estrogen therapies) and that sexual functioning also improved in the intervention group; however, quality of life (as measured by energy/vitality) did not differ between the two treatment groups. Several publications/papers have resulted from this research with others in preparation that will be submitted shortly. The findings from this study suggest that it is feasible to provide effective relief of menopausal symptoms in breast cancer survivors with non-estrogen alternatives.

14. SUBJECT TERMS
Breast Cancer, Menopause, Tamoxifen, Clinical Trials

15. NUMBER OF PAGES
93

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

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Patricia Young 10/8/99

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INTRODUCTION

Breast cancer is the leading cause of cancer in women, affecting 1 in 9 women in the US. According to the most recent SEER data, women with breast cancer have a relative 5-year survival rate of over 75%. Earlier detection of breast cancer, as well as improvements in post-operative adjuvant therapies, have enhanced the long term survival for women with this diagnosis. Symptoms of estrogen deprivation commonly occur in breast cancer survivors as a result of natural menopause, or menopause that is precipitated prematurely by chemotherapy or anti-estrogen therapy with tamoxifen. Hormone replacement therapy, the most efficacious treatment for these symptoms, is generally contraindicated in breast cancer survivors because of its potential risk of inducing a recurrence of breast cancer. Thus, many breast cancer survivors endure considerable morbidity and impaired quality of life (QL) as a result. This research program evaluated the role of a comprehensive menopausal assessment (CMA) and intervention program for management of menopausal symptoms in breast cancer survivors. We used a randomized, controlled design, assigning moderately symptomatic postmenopausal breast cancer survivors to an experimental or usual-care group. The experimental group received immediate assessment and intervention for their symptoms while the control group received no menopause related intervention during a four month period of observation. Systematic assessment of each breast cancer survivor assigned to the intervention permitted treatment of multiple symptoms simultaneously with a variety of non-hormonal pharmacologic, educational and behavioral interventions. The intervention program was provided by a nurse practitioner and is suitable for use in a primary care or oncology setting. The women who participated in this study were evaluated from a psychosocial and biomedical perspective, providing a rich data set on the problems that they experienced. The results of the study available thus far will be described in detail in the following sections, along with appended manuscripts. Other manuscripts are in preparation that will complete the reporting from this research project. The results from this study can have immediate impact on the management of women with breast cancer.

STATEMENT OF WORK

Task 1: Start-up Activities- finalize research instruments, develop and finalize intervention materials, develop and institute subject recruitment procedures.

Task 2: Conduct Randomized Controlled Trial-continuously screen and recruit eligible subjects; randomize subjects and collect follow-up data.

Task 3: Data Collection and Management-clean and edit data as it is collected.

Task 4: Data Analysis-analyze outcome data for randomized controlled trial; prepare manuscripts for publication; prepare final report.

All of the tasks planned in the statement of work have been accomplished, with additional manuscripts in preparation.

RESULTS

1. Is a comprehensive menopausal assessment (CMA) and intervention program effective in reducing menopausal symptoms and improving quality of life in postmenopausal breast cancer survivors?

The results from this study question are detailed in the appended manuscript (Appendix 1) that has been submitted for publication and is currently under review. The study sample will be described below, and the main findings of the study will be described. Readers are referred to Appendix 1 for a more detailed description of the study methods and analyses.

Study participants

Between January 31, 1996 and September 23, 1998 we entered 76 eligible women into the randomized trial. Recruitment of women for this trial was substantially more difficult than was anticipated. Figure 1 shows the flow of participants from screening and eligibility, through randomization, treatment, and completion of the study. We screened 197 women by telephone who met the minimum eligibility with regard to breast cancer diagnosis (free of cancer and at least eight months and no more than five years after the diagnosis of stage I or stage II breast cancer). Among these women, 98 (50%) were deemed ineligible, with the most common reasons being inadequate severity of target symptoms (35%), refusal to consider a pharmacological agent for relief of symptoms (33%), being medically ineligible (serious medical conditions, diagnosed more than 5 years earlier, on ERT, not menopausal) (18%), and the remainder for a variety of other reasons. We screened 99 potential participants who came for an in-person visit with the study nurse practitioner. After a more thorough assessment of the target symptoms and eligibility for the study, an additional 23 women were excluded for the following primary reasons: current symptoms of a major depression (35%), target symptoms were too mild (26%), and the remainder for a variety of other reasons including poor compliance with data collection, medically ineligible, transportation problems, and being too busy to participate in a research study. Ultimately, 76 women were randomized with 39 assigned to usual care and 37 assigned to intervention. There were four dropouts during the course of the follow-up (no follow-up data collected) and all occurred in the intervention condition: 2 were because of a family member's illness and 2 women became medically ineligible because of the development of metastatic disease, leaving a final sample of 39 women in usual care and 33 women in intervention. A post-hoc power calculation confirmed that comparing groups of size 39 and 33 would provide in excess of 80% power for detecting a difference of 0.75 standard deviations in each of the primary outcomes at the 0.025 significance level.

The medical and demographic characteristics of the 72 women who participated in this study and were evaluable are shown in Table 1. On average, these women were 54.5 years old and were 2.5 years since the time of their breast cancer diagnosis. They had been postmenopausal for about 7 years and about 57% of them had taken hormone replacement in the past. The majority of the women were married, well educated, and affluent, being demographically similar to other samples of breast cancer patients we have studied with the exception of being 90% white. Two thirds of the women had received a lumpectomy with radiation as their primary treatment, and 56% of them were on tamoxifen at the time they entered this study. The treatment and usual care groups were balanced on all factors with the exception of race/ethnicity, where by chance more of the non-white participants were assigned to the treatment condition.

In Table 2 we present results from the instruments used for the outcome assessments in this trial. Overall, these women exhibited high levels of functioning and quality of life, comparable to what we have seen in other samples of breast cancer survivors (1,2). The scores on the RAND 36-item health survey are at or above the mean for the general population of healthy women (3), which is confirmed by the Composite Physical and Mental Health Scales that are nearly 50, which is the median score for the general population. The two study groups scored similarly on all of the RAND scales with the exception of the Vitality scale, for which the usual care group had a significantly lower baseline score ($p=0.05$).

The women who participated in this study were highly symptomatic with respect to the target menopausal symptoms. Twenty-seven of the 72 (38%) had all three target menopausal symptoms. An additional 32 of the 72 (44%) had two of the three target menopausal symptoms. Only 18% had a single target symptom. Overall, hot flashes were the most common target symptom (97% of study participants) followed by vaginal dryness (71%) and urinary incontinence (51%). The mean severity score for each symptom (hot flashes, vaginal symptoms, urinary symptoms), as well as the composite symptom scale score are shown in Table 2. In addition to being the most prevalent symptom, hot flashes were rated as the most severe (2.6 on a scale of 0 to 4) in both the intervention and usual care groups. Although the severity of urinary symptoms was significantly worse in the usual care group, the composite symptom scale score was not significantly different between the two study groups. At baseline, in spite of having moderate to severe menopausal symptoms, these breast cancer survivors reported normal QL on a standardized generic measure of health-related quality of life (Table 2). Sexual functioning was the only summary scale on the CARES to demonstrate moderate problems. We explored the correlations between symptoms and the RAND Health Survey and there were no significant correlations.

Description of the Intervention

Our intervention was provided by a nurse practitioner, who in her clinical visit with the patient provided a structured, comprehensive assessment of the three menopause-related target symptoms: hot flashes, vaginal dryness, and stress urinary incontinence. The assessment was followed by an individualized plan of education, counseling, pharmacological and/or behavioral interventions, psychosocial support, referrals, and follow-up, tailored to each woman's needs and preferences. The purpose of the intervention was to provide these symptomatic patients with the information, skills, medication and/or support they needed to manage their symptoms more effectively.

The structured, comprehensive assessment consisted of three components: 1) a review of self-monitoring results (symptom diary cards), 2) an in-depth interview focusing on target symptoms and influencing factors, and 3) a standardized psychosocial evaluation. First, self-monitoring of target symptoms was accomplished through the diary cards that were completed for 28 days prior to receiving the intervention. On each card, the woman noted the timing and duration of the target symptoms, and rated the severity on a numerical scale from "1" (mild) to "4" (severe), and degree of disruption/distraction experienced, also on a numerical scale from "0" (not at all) to "4" (very much). There was a section on the card for the woman to comment on her symptoms (e.g., what she was doing or feeling when the symptoms occurred). There was also a checklist of physiologic responses associated with hot flashes, completed once on the 28th day.

Second, expanding upon the information recorded on the diary cards, the nurse practitioner interviewed each woman regarding key aspects of her symptom experience, including her description of her symptoms, her responses to those symptoms (physiological, psychosocial, and behavioral), and how

these symptoms and/or responses bothered her or disrupted her daily functioning (4). During the study visit, the nurse practitioner conducted a detailed interview to obtain information regarding any exacerbating or ameliorating factors, including past or current symptom management strategies (e.g., lifestyle or behavioral interventions, herbal or dietary supplements, other alternative/complementary therapies, and/or prescription medications).

Finally, the psychosocial evaluation consisted of a self-administered, standardized questionnaire, the Cancer Rehabilitation Evaluation System (CARES). Problems rated a 3 or greater were briefly explored by the nurse practitioner and any relationship to target symptoms was noted (e.g., vaginal dryness and sexual dysfunction). These problems were then addressed as part of the education and counseling component of the intervention. The education and counseling focused on providing the woman with the information and/or skills she needed to manage her symptoms more effectively. The content of the education and counseling was semi-structured, varying to some degree for each woman according to her specific symptoms, psychosocial concerns, informational needs (desire for information), and preference for participation in the decision making process (5). Each woman received individualized information about the following topics, as appropriate: 1) the physiologic changes underlying the target symptoms, 2) the potential relationship of target symptoms to other symptoms (e.g., hot flashes and difficulty sleeping or vaginal dryness and sexual dysfunction), 3) potential influencing factors (e.g., ambient temperature, stress, etc.), and 4) health promoting lifestyle/behavioral interventions (e.g., exercise, weight and stress management, and smoking cessation). In addition, each woman received educational pamphlets and individualized counseling regarding the benefits, side effects, and use of any recommended pharmacological or behavioral interventions, as appropriate. All women received a folder containing written materials, including several available pamphlets on target symptoms and sexuality after cancer, a list of self-help books on psychological and sexual health after breast cancer, and a brochure about a resource center for women with cancer. Additional general information about hormone replacement therapy after breast cancer, the use of alternative treatments for menopausal symptoms, and the role other factors (developmental, psychological, social, and cultural) in an individual's life may have on her experience of symptoms and health-related quality of life was also provided. Decision support therapy (6) was provided as necessary.

Pharmacological options included the use of transdermal clonidine (Catapress TTS), megestrol acetate (Megace), and Bellergal for hot flashes (7), the use of Astroglide and/or Replens for vaginal dryness (7), and phenylpropanolamine for stress urinary incontinence (8). Two behavioral interventions were also offered: paced respiration for hot flashes (9) and pelvic floor muscle exercises for stress urinary incontinence (10). The choice of a specific pharmacological and/or behavioral option was based on the absence of any contraindications for its use and a woman's preference for trying a specific option.

The psychosocial component of the intervention consisted of identifying psychosocial problems using the CARES, listening to the problem, determining if the woman wanted help with the problem, providing information, reassurance, and/or referral to self-help or professional resources, as appropriate. Women with multiple psychosocial problems rated as 3 or greater were referred to a psychologist for individual counseling.

Follow up included a telephone call two weeks after the intervention visit to assess for potential side effects and/or any problems with the recommendations. It also included an interim visit at two

months and a final visit at four months to evaluate her response to the individualized plan. Interventions were adjusted, discontinued, or added, as appropriate.

Outcomes

At the end of the four month study period we found that women who received the intervention had a highly significant decrease in their composite symptom score ($p=0.0004$), with the group receiving the intervention having a follow-up symptom score that was 43% lower than the usual care group. For the quality of life endpoint, energy/vitality, we could demonstrate no significant benefit in the intervention group in comparison to the usual care group. Our secondary and exploratory endpoint was sexual functioning. For this outcome we found significant improvement in the women who were assigned to the CMA intervention ($p=0.04$), with the intervention group having a reduction in the severity of sexual problems by about 39% compared to the usual care group.

2. How does menopause affect vaginal health?

For a detailed report on these results, the reader is referred to appended material (Appendix #2), which contains a manuscript that is in press in the journal *Climacteric*. The major findings from this evaluation will be described briefly below. This was primarily a methodological study that focused on the development of a physical examination method to accurately describe the presence or absence of vaginal atrophy and inflammation.

The assessment of vaginal atrophy is central to menopause-related research and clinical practice. However, methods of assessing vaginal atrophy have not been systematically described. As part of this program of research, we developed a clinical assessment scale for evaluation of vaginal atrophy and inflammation on clinical examination, and then compared our clinical evaluation to patient report of symptoms as well as cytological examination of vaginal smears and measurement of vaginal pH. We studied this in forty postmenopausal breast cancer survivors who were not on tamoxifen. Our physical examination scale for atrophy was moderately reliable and was statistically significantly correlated with pH and parabasal cells on cytology. While the physical examination inflammation scale also had good reliability, it was not significantly associated with findings of inflammation on vaginal smear. There was excellent concordance between two raters with regard to the physical examination ratings of inflammation and atrophy. Self-reported symptoms of vaginal itching/irritation or vaginal dryness were poorly related to findings on the physical examination. This discordance is explored further in the appended manuscript.

3. How can a clinician (nurse practitioner or primary care provider) effectively assess and provide intervention for menopausal symptoms in breast cancer survivors?

A manuscript is currently in preparation describing in great detail the assessment procedures and interventions that were used in this study. This report will be sent to a cancer nursing journal.

4. What is the relationship between sexual functioning and menopausal symptoms, hormone levels, and vaginal health in postmenopausal breast cancer survivors?

Both Drs. Ganz and Greendale have conducted empiric research on this topic in breast cancer survivors and healthy postmenopausal women (1,11,12). The detailed assessment methodology of the current study provided an opportunity to expand their previous work to include measurement of reproductive hormones and clinical and cytologic evaluations of vaginal health. The results of these studies in the study sample are being described in a manuscript that is currently in preparation.

5. What is the relationship between a daily diary report of menopausal symptoms (hot flashes, vaginal dryness, urinary incontinence) and self-report of the severity of these symptoms retrospectively evaluated?

This paper is planned but the analyses have not yet been completed. It constitutes another methodological contribution to the measurement of symptoms in this population of women. The research participants completed a set of diary cards during two different 28 day periods and at the conclusion of each of those periods rated a symptom severity scale for the preceding 4 weeks. The relationship between these two evaluation methods have not been studied, to the best of our knowledge, and could provide important calibration for the severity scale that was rated. That is, a severity symptom of "1" might indicate a hot flash every other day, whereas a score of "4" might indicate an average of 5 hot flashes each day. The findings from this study will be important as a validation of the severity scale in future research.

KEY RESEARCH ACCOMPLISHMENTS

- Development of an intervention program to alleviate menopausal symptoms in breast cancer survivors
- Successful completion of a randomized, controlled trial that tested the efficacy of the intervention on outcomes of symptoms, quality of life, and sexual functioning
- Development and reliability/validity assessment of a physical assessment scale for vaginal health in postmenopausal women
- Description of the severity and frequency of menopausal symptoms in breast cancer survivors
- Examination of sexual functioning in relationship to psychological well-being, dyadic adjustment, vaginal symptoms, hormones, and vaginal health

REPORTABLE OUTCOMES

- 2 manuscripts accepted for publication and 1 submitted; 3 additional manuscripts in preparation or planned; 1 presentation at the DOD Era of Hope meeting
- Two funded projects (NCI and DOD) examining the late reproductive health effects of breast cancer treatment in women were 50 years or younger at the time of diagnosis

CONCLUSIONS

This research study has demonstrated that it is possible to achieve a significant reduction in menopausal symptoms in moderately symptomatic breast cancer survivors through use of a clinical

intervention that used education, counseling and non-estrogen pharmacological agents to address the target symptoms. While quality of life did not improve significantly as a result of the intervention, sexual functioning did. This latter finding is very important, since breast cancer survivors frequently report sexual problems. In a previous study, we demonstrated that a major contributor to sexual dysfunction was the presence of vaginal dryness (12) and recommended that interventions to address this problem should be tested for their impact on sexual functioning. Indeed, this randomized, controlled trial demonstrates the efficacy of an intervention that targeted vaginal dryness on improving sexual functioning.

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Figure 1: Study Recruitment Flow Chart

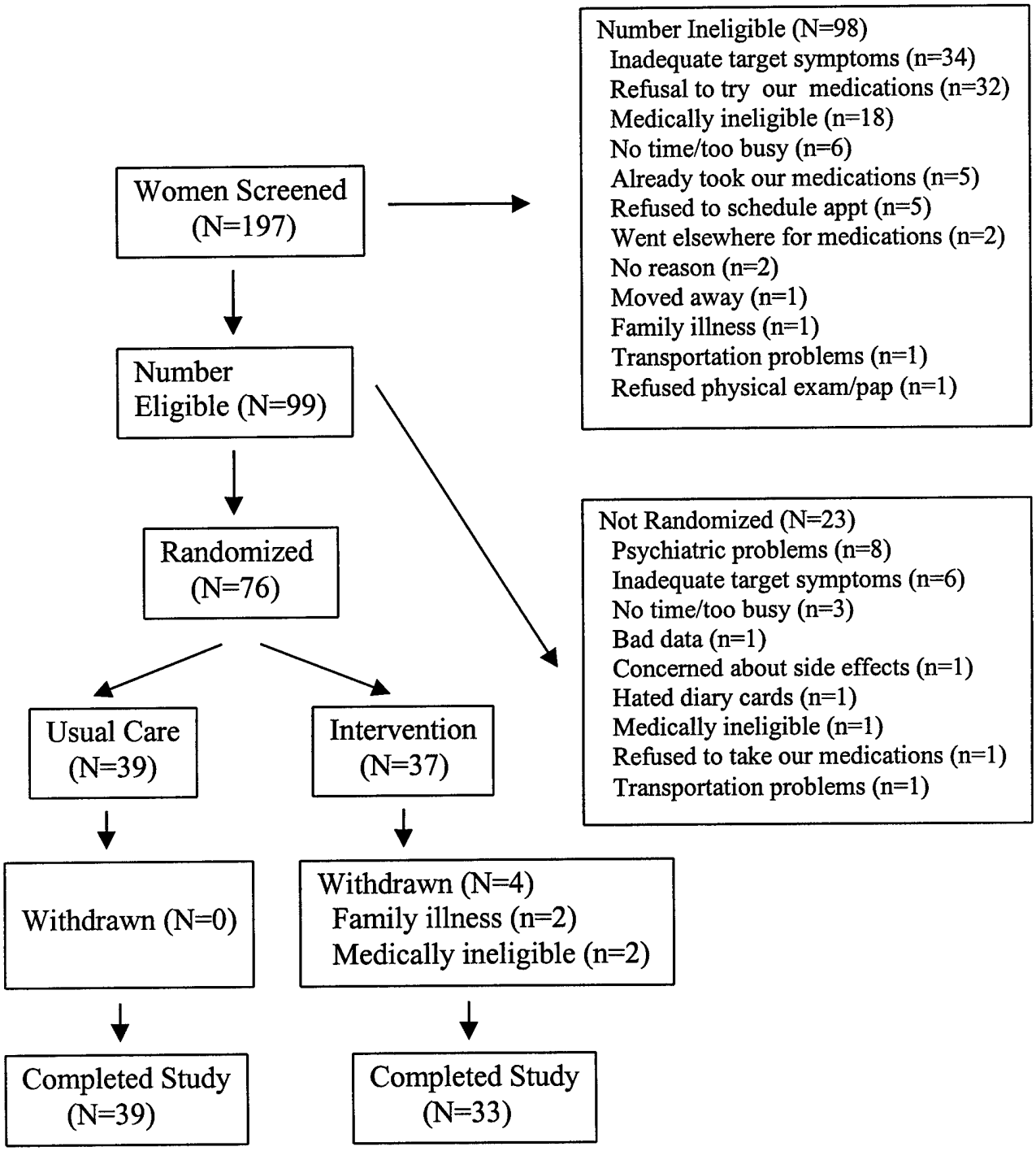

Table 1: Baseline Medical/Demographic Characteristics N=72 Women Means (Standard Deviations) for Continuous Variables and Frequencies (Percentages) for Categorical Variables

	Usual Care Group	Intervention Group	All Women	p-value[1]
Age	54.5 (5.5)	54.6 (6.4)	54.5 (5.9)	.91
Yrs Since Dx	2.6 (1.4)	2.4 (1.3)	2.5 (1.3)	.50
Years Since LMP[2]	7.2 (7.7)	6.5 (6.8)	6.9 (7.3)	.67
Ever Taken HRT[3]	23 (59%)	18 (55%)	41 (57%)	
Ethnicity				
Asian	0 (0%)	1 (3%)	1 (1.5%)	
Black	1 (3%)	4 (12%)	5 (7%)	.026
Hispanic	0 (0%)	1 (3%)	1 (1.5%)	(white vs.
White	38 (97%)	27 (82%)	65 (90%)	non-white)
Marital Status				
Married	32 (82%)	27 (82%)	59 (82%)	.980
Not Married	7 (18%)	6 (18%)	13 (18%)	
Education				
Less Than College	16 (41%)	13 (39%)	29 (40%)	
College Grad	13 (33%)	13 (39%)	26 (36%)	.843
Advanced Degree	10 (26%)	7 (21%)	17 (24%)	
Employment				
Employed Full-time	21 (54%)	18 (55%)	39 (54%)	
Employed Part-time	7 (18%)	9 (27%)	16 (22%)	.482
Not Employed	11 (28%)	6 (18%)	17 (23%)	
Income				
<$45,000/year	10 (26%)	7 (21%)	17 (23%)	
$45,000-$75,000/year	11 (28%)	10 (30%)	21 (29%)	.907
>$75,000/year	18 (46%)	16 (48%)	34 (47%)	
Type of Surgery				
Lumpectomy	25 (66%)	22 (67%)	47 (66%)	.938
Mastectomy	13 (34%)	11 (33%)	24 (34%)	

[1] T-tests for continuous variables, chi-square tests for categorical variables
[2] LMP=last menstrual period
[3] HRT=hormone replacement therapy

Table 1 Continued

Cancer Treatments							
Tamoxifen use	24	(62%)	16	(48%)	40	(56%)	.267
Prior Radiation	24	(62%)	26	(79%)	50	(69%)	.113
Prior Chemotherapy	18	(46%)	16	(48%)	34	(47%)	.844
Medical Conditions							
Arthritis	11	(28%)	10	(30%)	21	(29%)	.845
Heart Disease	0	(0%)	1	(1%)	1	(1%)	n/a
Hypertension	4	(10%)	5	(15%)	9	(12.5%)	n/a
Diabetes	0	(0%)	0	(0%)	0	(0%)	n/a
Psych difficulties	2	(5%)	4	(12%)	6	(8%)	n/a
Alcohol problems	0	(0%)	0	(0%)	0	(0%)	n/a
Drug problems	0	(0%)	0	(0%)	0	(0%)	n/a
Other conditions[4]	9	(23%)	6	(18%)	15	(20%)	.610

[4] These include: osteoporosis, fibromyalgia, hypothyroidism, asthma, allergic rhinitis, ileostomy, mitral valve prolapse, ulcer, and chronic canker sores

Table 2: Baseline Scale Values for N=72 Women
Means (Standard Deviations)*

	Usual Care Group (n=39)	Intervention Group (n=33)	All Women (n=72)	p-value
Symptom Scores				
Hot flashes	2.63(1.1)	2.57(1.2)	2.60 (1.12)	.84
Vaginal	1.06(0.9)	1.08(1.1)	1.07 (1.01)	.93
Urinary	0.76(1.0)	0.39(0.5)	0.59 (0.82)	.05
Symptom scale score	**1.42(0.56)**	**1.31(0.62)**	**1.37(0.59)**	**.44**
RAND 36-item Health Survey				
Physical Functioning	84.9(14.6)	85.6(18.5)	85.2(16.4)	.85
Role Limits - Physical	85.9(24.2)	83.3(29.1)	84.7(26.4)	.68
Role Limits - Emotional	76.9(31.7)	81.8(35.4)	79.2(33.3)	.54
Vitality	**56.7(22.2)**	**66.5(20.3)**	**61.2(21.7)**	**.05**
Emotional Well-being	76.3(12.0)	79.4(15.2)	77.7(13.5)	.34
Social Functioning	85.6(16.6)	89.4(19.3)	87.3(17.9)	.37
Pain	81.1(20.1)	80.6(19.3)	80.9(19.6)	.92
General Health	77.4(17.2)	80.6(17.9)	78.9(17.4)	.45
Composite Scales				
Physical	52.0(6.8)	51.6(7.4)	51.8(7.0)	.83
Mental	49.1(7.8)	52.1(9.5)	50.5(8.7)	.14
CARES Scores				
Global	0.55(0.32)	0.51(0.40)	0.53(0.36)	.68
Physical	0.40(0.42)	0.41(0.42)	0.40(0.46)	.91
Psychosocial	0.61(0.39)	0.63(0.54)	0.62(0.90)	.86
Marital	0.43(0.49)	0.26(0.35)	0.35(0.44)	.07
Sexual	**1.36(0.91)**	**1.26(0.91)**	**1.32(0.90)**	**.64**
Medical Interaction	0.33(0.45)	0.18(0.35)	0.26(0.42)	.15

*Scales indicated in bold are the primary and secondary outcomes for the study

PERSONNEL SUPPORTED BY THIS RESEARCH

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APPENDICES

1. Ganz PA, Greendale GA, Petersen L, Zibecchi L, Kahn B, Belin TR. Managing Menopausal Symptoms in Breast Cancer Survivors: Results of a Randomized Controlled Trial. Submitted to JNCI.

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APPENDIX 1

Managing Menopausal Symptoms in Breast Cancer Survivors: Results of a Randomized Controlled Trial[1]

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1. Supported by US Army Breast Cancer Research Program grant number DAMD 17-94-J-4507

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Running title: Intervention for menopausal symptoms after breast cancer

Word count: 6,485

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ABSTRACT

Background: Menopausal symptoms (hot flashes, vaginal dryness, urinary incontinence) are very common in breast cancer survivors and cannot be managed with standard estrogen replacement therapy (ERT).

Objective: To test the efficacy of a Comprehensive Menopausal Assessment (CMA) in achieving relief of symptoms, improvement in quality of life and sexual functioning.

Design: Randomized, controlled trial.

Setting: Cancer center in an urban metropolitan area.

Patients: Seventy-two postmenopausal breast cancer survivors with at least one severe menopausal target symptom.

Intervention: Nurse practitioner-delivered assessment and intervention that provided education and counseling, as well as pharmacological and behavioral interventions for three target menopausal symptoms. Intervention period was over four month period of time.

Measurements: Composite menopausal symptom scale, RAND Short Form Health Survey Vitality Scale, CARES Sexual Functioning Scale at baseline and four-month follow-up.

Results: Patients receiving the intervention demonstrated significant improvement in menopausal symptoms, but no significant change in vitality. Sexual functioning was significantly improved in the treatment group compared to the usual care group.

Conclusions: A clinical intervention program for menopausal symptom management in breast cancer survivors is feasible and acceptable to patients, leading to reduction in symptoms and improvement in sexual functioning. Measurable improvement in a general quality of life measure was not demonstrated.

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women, with about 175,000 cases diagnosed each year in the United States (1). There are estimated to be more than 2 million breast cancer survivors today (2). These numbers will continue to increase due to the recent decline in breast cancer mortality reported over the past 4 years (3). The improvements in survival are attributed to a combination of the more widespread application of mammographic screening, as well as the dissemination of effective adjuvant therapies.

Breast cancer is primarily a disease of postmenopausal women in whom the breast cancer diagnosis often coincides with ongoing menopausal symptoms such as hot flashes, vaginal dryness, change in mood, and urinary incontinence. Many of these women will be taking estrogen replacement therapy (ERT) for alleviation of symptoms or for its long-term purported preventive benefits. Breast cancer patients on ERT at the time of diagnosis are usually told to stop the ERT as soon as the cancer diagnosis is made. As a result, they often experience a recurrence of vasomotor symptoms at the same time that they are dealing with the shock of the cancer diagnosis. If the woman requires adjuvant therapy with either tamoxifen or chemotherapy, she may have additional treatment related side effects to deal with at the same time. Tamoxifen, in particular, increases the frequency and severity of hot flashes (4-6). Clinically, tamoxifen therapy in postmenopausal women has been associated with both vaginal dryness and increased vaginal secretions. However, recent data from the NSABP Breast Cancer Prevention Trial, which compared tamoxifen to placebo in healthy women at high risk for breast cancer, did not demonstrate excess vaginal dryness in the women taking tamoxifen (6). However, women in all age groups on tamoxifen experienced more frequent hot flashes, night sweats, and vaginal discharge than women taking placebo (6). The vaginal dryness that occurs in postmenopausal breast cancer survivors most likely relates to age-related loss of natural endogenous estrogen (7).

For the pre- and perimenopausal breast cancer patient, there are other special considerations. Chemotherapy is the primary form of adjuvant therapy for younger women with breast cancer. Treatment with the alkylating agent cyclophosphamide hastens ovarian failure in many women (8). While ovarian failure as a result of alkylating agents can occur at any age, it is most common in women older than 40 years and least likely in women less than 30 years (8). Anovulation secondary to chemotherapy can be transient or permanent, but many women will stop menstruating within the first few cycles of chemotherapy and then never resume menstruation. Under these circumstances, women receiving cytotoxic chemotherapy are thrown into menopause abruptly, with symptoms as profound as those associated with surgical castration. Menopause symptoms usually come without much warning, and add to the psychological and physical burdens associated with the recent breast cancer diagnosis and surgery.

Few studies have directly examined the relationship between menopausal symptoms and quality of life in healthy women or women with breast cancer (9-12). Intuitively, symptoms that disrupt sleep, affect mood, or may cause discomfort or embarrassment may be likely to influence aspects of health-related quality of life, such as physical, emotional or social well-being, and vitality (11). However, there is little empiric research on this question in breast cancer survivors. Similarly, there is little information on the relationship of menopausal symptoms and breast cancer to sexual functioning. The relation between menopause, sex steroids, and sexual motivation ("libido") remain controversial (13), but this aspect of sexuality may also be affected by ovarian failure. The vaginal epithelium may become atrophic leading to clinical symptoms of vaginal dryness and dyspareunia. In a previous study, we surveyed a large sample of breast cancer survivors who were assessed on average 3 years after their breast cancer diagnosis (12). We found that sexual functioning in these women was very similar to healthy volunteer women participating in the Postmenopausal Estrogen Progestin Intervention (PEPI) trial (12,14). However, the breast cancer survivors reported higher rates of hot flashes and vaginal dryness than age-matched healthy controls (12,14). Although the benefit-risk

ratio of ERT in breast cancer survivors is being re-evaluated (15), its use in this group remains highly controversial. Therefore, these patients are often at a loss for what to do for menopause symptom management.

Several studies and randomized trials have evaluated the efficacy of the different non-ERT pharmacological approaches to the management of vasomotor symptoms (16-19), and urogenital atrophy (20-22). These studies provided the building blocks for our development of a strategy to address these symptoms together, with the goal of providing a comprehensive assessment and management program for breast cancer survivors who were enduring disruptive menopause-related symptoms. Modeled after the "Comprehensive Geriatric Assessment"(CGA) (23-25) we developed an intervention called the "Comprehensive Menopausal Assessment" (CMA). Research in CGA has shown that a more substantial benefit is obtained if CGA is used in subjects who need it most, hence the term targeting (26). Setting certain criteria for admission to the CGA protocol allows the population to be matched to the resources the program can reasonably deliver. If patients are too ill (i.e., near death), or too well (i.e., not in need of much improvement), it is unlikely that a CGA will serve them well. Like the geriatric approach, our CMA intervention was designed to assess systematically three target menopausal symptoms— hot flashes, vaginal dryness and stress urinary incontinence—with the goal of providing focused non-ERT interventions for each target symptom, depending on the presence, frequency and severity of each symptom. The specific interventions for each symptom complex were formalized and were provided to the woman as long as she wanted help with relief of the symptom for the duration of the study. Our endpoints were relief of symptoms and improvement in health-related quality of life. This report describes the results of a randomized controlled trial designed to evaluate the efficacy of the CMA intervention in postmenopausal breast cancer survivors.

METHODS

Subject Eligibility and Recruitment

Peri- and postmenopausal breast cancer survivors with at least one of three target symptoms (hot flashes, vaginal dryness, stress urinary incontinence) were the participants in this research study. Eligibility criteria were as follows: 1) participants must be female breast cancer survivors who were free of cancer and at least eight months and no more than five years after the diagnosis of stage I or stage II breast cancer; 2) participants must be peri- or postmenopausal (defined by amenorrhea of six months or more); 3) participants must have completed any chemotherapy or radiation therapy at least four months prior to enrollment, but could be taking tamoxifen; 4) participants must have had at least one target symptom under investigation (hot flashes, vaginal dryness, stress urinary incontinence) that was by self-report moderate to severe in intensity; 5) and the participant must have had at least one target symptom that she perceived to be troublesome enough to warrant treatment with a study medication.

Exclusion criteria were: 1) a history of other cancers, with the exception of non-melanoma skin cancer; 2) serious chronic medical conditions that might influence the assessment of health-related quality of life, e.g. severe rheumatoid arthritis, stroke, chronic lung disease; 3) an abnormal PAP smear (dysplasia or greater); 4) current symptoms of a major psychiatric illness (e.g., depression) that were not being treated, or if on psychotropic medications, not controlled; 5) inability to read and write in English; 6) active alcohol or substance abuse; 7) use of ERT within the past three months; 8) major cognitive impairment or inability to provide informed consent.

Participants were recruited through brochures placed in the offices of community oncologists and surgeons, as well as through paid newspaper advertisements and notices in hospital newsletters. Potential participants were first screened for eligibility using a telephone interview. Eligible women were invited to an in-person-screening visit, at which time informed consent was obtained and a brief physical examination and

Pap smear were performed. During the examination, women were evaluated for study eligibility, as outlined above. Women who remained eligible and interested in the study after the in-person screening visit were asked to complete a trial run of the study's daily symptom diary for each target symptom during the next four weeks (see description of diary cards below). Final determination of study eligibility occurred after review of the Pap smear results and evaluation of compliance with completion of the diary cards as part of a run-in period (80% completion of diary cards was required for study enrollment).

Study design and procedures

This study was a randomized controlled trial in which breast cancer survivors between 8 months and 5 years post diagnosis, with at least one severe target menopausal symptom, were assigned to receive either usual care or the CMA intervention program. Subjects assigned to usual care received the CMA intervention at the end of the study, as part of a wait-list control design. The institutional review board approved the study and all subjects provided written informed consent.

Women who successfully completed the run-in period and had no exclusionary conditions were invited for a second in-person baseline study visit. At that time they signed an informed consent for the full study, had blood drawn for hormone and cholesterol tests, and answered a 29-page questionnaire that included items on basic medical and demographic information and health history, symptoms, and quality of life. Women were then randomly assigned to either the usual care group or the CMA intervention group. Randomization was stratified by age ($\leq$55 vs. >55) and tamoxifen use (currently using vs. not). Women who were assigned to the usual care group were thanked for completing the baseline information and told that their condition would be tracked during the following four months, after which time they would be debriefed and given additional information about relief for their symptoms. Women who were assigned to the CMA intervention group were immediately given the intervention (see description of the intervention below).

Two months after the baseline visit, women in the usual care group received a phone call to ask about any therapies (medications, vitamins, herbs, or psychosocial remedies) they may have used to help manage their symptoms. Women in the intervention group were asked to come in for a 2-month follow-up, in-person visit. At this visit their target symptoms were re-evaluated, their study medications and potential side effects were re-assessed, they completed a psychosocial screening instrument, and they were asked about therapies they may have initiated on their own, apart from the recommended study interventions. Medications were adjusted, discontinued, or changed at this time if necessary.

One month later, all women were sent a second diary card packet to fill out during the 28 days prior to their final visit that occurred at four months after the baseline visit. At the final study visit, all women had a gynecological exam including Pap smear and were asked to fill out the same questionnaire battery used at baseline. After completion of the questionnaire, women in the usual care group were given information about the CMA interventions that pertained to their menopausal symptoms. Women in the CMA group were thanked for their participation and they were subsequently sent a letter summarizing our evaluation of their symptoms and treatment recommendations, with the suggestion that they contact their physician for continuation of any medications started as part of the CMA.

Outcome Measures

Menopausal Symptom Checklist adapted from the Breast Cancer Prevention Trial (BCPT) Symptom Checklist. The BCPT Symptom Checklist is a 43-item list of commonly reported physical and psychological symptoms (e.g., nausea, headaches, vomiting, diarrhea, short temper, tendency to stay in bed), as well as symptoms that have been associated with the menopause (e.g., hot flashes, joint pains, forgetfulness, difficulty concentrating, vaginal dryness) and tamoxifen use (e.g., vaginal discharge). This checklist was developed specifically for the BCPT (7), which expanded and modified a list developed for the PEPI Trial (27,28). For each item the woman was asked to rate how bothered she was by any of the everyday

problems during the past 4 weeks, using a 5 point Likert scale of severity that ranged 0 (not at all) to 4 (extremely). From the checklist, we selected seven symptoms that assessed the target menopausal symptoms being studied in this trial. The items were "hot flashes" and "night sweats" (Hot flash subscale), "vaginal dryness," "genital itching/irritation" and "pain with intercourse" (Vaginal subscale); and "difficulty with bladder control while laughing or crying" and "difficulty with bladder control at other times" (Urinary subscale). We constructed a summary scale for all seven symptoms by summing the individual severity scores and determining the mean severity score for the 7 items. The Cronbach alpha scores for each subscale, respectively were Hot flash subscale =0.76; Vaginal subscale = 0.73; Urinary subscale = 0.76; and for the Summary Scale of all symptoms =0.50. These results show high internal consistency reliability for the individual subscales and adequate internal consistency reliability for the summary scale.

Vitality Scale from the RAND 36-item Health Survey 1.0 (alternatively known as Medical Outcomes Study (MOS) SF-36). The entire RAND 36-item health survey was administered as a generic measure of health-related quality of life (29,30). The Vitality Scale, which is strongly correlated with both the physical and emotional dimensions of health-related quality of life, was selected as the primary quality of life outcome for the trial. The Vitality Scale contains 4 items and is scored from 0 to 100, with 100 indicating the highest energy and 0 indicating the lowest energy or greatest fatigue. The RAND 36-item Health Survey contains 8 individual subscales that are part of the three general areas of health related quality of life. Each subscale ranges from 0 to 100 with 100 being the most favorable score. The subscales are physical functioning, role function-physical, bodily pain, social functioning, mental health, role function-emotional, vitality, and general health perceptions (30). The instrument can also be scored as two component summary scales for physical health and mental health, whose median score for the population is 50.

Sexual Summary Scale from the Cancer Rehabilitation Evaluation System (CARES). The CARES is a self-administered survey instrument that assesses the quality of life and rehabilitation needs of

cancer patients (31,32). The CARES has excellent reliability, validity and psychometric properties (33). Although the CARES is a generic, cancer-specific quality-of-life measure (34), extensive normative data are available in breast cancer patients (12,35,36). Scoring of the CARES generates a Global Score or 5 higher-order factors (Physical, Psychosocial, Medical Interaction, Marital and Sexual). We explored sexual functioning as a secondary outcome in this randomized trial, hypothesizing that improvements in the target menopausal symptoms would lead to increased vitality and decreased vaginal dryness, thus facilitating improved sexual functioning. The Sexual Summary Scale from the CARES includes 8 items. Four items apply to all women, while the other 4 items only apply to women who have been sexually active with a partner since their cancer diagnosis. In this study, we also used the CARES to facilitate psychosocial screening and evaluation as part of the intervention.

Description of the CMA Intervention

We used a case management intervention, conducted by a nurse practitioner, that focused on a structured, comprehensive assessment of the three menopause-related target symptoms: hot flashes, vaginal dryness, and stress urinary incontinence. The assessment was followed by an individualized plan of education, counseling, pharmacological and/or behavioral interventions, psychosocial support, referrals, and follow-up, tailored to each woman's needs and preferences. The purpose of the intervention was to provide these symptomatic patients with the information, skills, medication and/or the support they needed to manage their symptoms more effectively.

The structured, comprehensive assessment consisted of three components: 1) a review of self-monitoring results (symptom diary cards), 2) an in-depth interview focusing on target symptoms and influencing factors, and 3) a standardized psychosocial evaluation. First, self-monitoring of target symptoms was accomplished through the diary cards that were completed for 28 days prior to receiving the intervention. On each card, the woman noted the timing and duration of the target symptoms, and rated the severity on a

numerical scale from "1" (mild) to "4" (severe), and degree of disruption/distraction experienced, also on a numerical scale from "0" (not at all) to "4" (very much). There was a section on the card for the woman to comment on her symptoms (e.g., what she was doing or feeling when the symptoms occurred). There was also a checklist of physiologic responses associated with hot flashes, completed once on the 28th day.

Second, expanding upon the information recorded on the diary cards, the nurse practitioner interviewed each woman regarding key aspects of her symptom experience, including her description of her symptoms, her responses to those symptoms (physiological, psychosocial, and behavioral), and how these symptoms and/or responses bothered her or disrupted her daily functioning (37). During the study visit, the nurse practitioner conducted a detailed interview to obtain information regarding any exacerbating or ameliorating factors, including past or current symptom management strategies (e.g., lifestyle or behavioral interventions, herbal or dietary supplements, other alternative/complementary therapies, and/or prescription medications).

Finally, the psychosocial evaluation consisted of a self-administered, standardized questionnaire, the Cancer Rehabilitation Evaluation System (CARES). Problems rated a 3 or greater were briefly explored by the nurse practitioner and any relationship to target symptoms was noted (e.g., vaginal dryness and sexual dysfunction). These problems were then addressed as part of the education and counseling component of the intervention.

The education and counseling focused on providing the woman with the information and/or skills she needed to manage her symptoms more effectively. The content of the education and counseling was semi-structured, varying to some degree for each woman according to her specific symptoms, psychosocial concerns, informational needs (desire for information), and preference for participation in the decision making process (38). Each woman received individualized information about the following topics, as appropriate: 1) the physiologic changes underlying the target symptoms, 2) the potential relationship of target symptoms to

other symptoms (e.g., hot flashes and difficulty sleeping or vaginal dryness and sexual dysfunction), 3) potential influencing factors (e.g., ambient temperature, stress, etc.), and 4) health promoting lifestyle/behavioral interventions (e.g., exercise, weight and stress management, and smoking cessation). In addition, each woman received educational pamphlets and individualized counseling regarding the benefits, side effects, and use of any recommended pharmacological or behavioral interventions, as appropriate. All women received a folder containing written materials, including several available pamphlets on target symptoms and sexuality after cancer, a list of self-help books on psychological and sexual health after breast cancer, and a brochure about a resource center for women with cancer. Additional general information was also provided about hormone replacement therapy after breast cancer, the use of alternative treatments for menopausal symptoms, and the role other factors (developmental, psychological, social, and cultural) have on symptoms and health-related quality of life. Decision support therapy (39) was provided as necessary.

Pharmacological options included the use of transdermal clonidine (Catapress TTS), megestrol acetate (Megace), and Bellergal for hot flashes (13), the use of Astroglide and/or Replens for vaginal dryness (13), and phenylpropanolamine for stress urinary incontinence (22). Two behavioral interventions were also offered: paced respiration for hot flashes (40) and pelvic floor muscle exercises for stress urinary incontinence (41). The choice of a specific pharmacological and/or behavioral option was based on the absence of any contraindications for its use and a woman's preference for trying a specific option.

The psychosocial component of the intervention consisted of identifying psychosocial problems using the CARES, listening to the problem, determining if the woman wanted help with the problem, providing information, reassurance, and/or referral to self-help or professional resources, as appropriate. Women with multiple psychosocial problems rated as 3 or greater were referred to a psychologist for individual counseling.

Follow up included a telephone call two weeks after the intervention visit to assess for potential side effects and/or any problems with the recommendations. It also included an interim visit at two months and a

final visit at four months to evaluate her response to the individualized plan. Interventions were adjusted, discontinued, or added, as appropriate.

Data Collection and Statistical Analysis

Quality of life and symptom outcome data were collected using self-administered questionnaires at the baseline and follow-up visits. Data on self-initiated therapies were collected at baseline, follow-up and once in between. For women in the CMA intervention group, data on use of recommended therapies and related side effects were collected four times, starting with a telephone call a few days after the baseline visit. The data were entered using Paradox 5.0 (Borland International, Inc., 1994), and analyzed using SAS statistical software (Version 6.04, SAS Institute Inc., Cary, NC).

When this trial was originally conceptualized in the early 1990's, the proposed primary outcomes were emotional well-being and overall quality of life, with sexual functioning as a secondary outcome. With emerging data from other research studies (7,42,43), it became clear that these dimensions of health-related quality of life were often quite stable over time, and did not reflect major differences in cancer treatment. As a result we proposed the use of the Vitality Scale of the RAND Health Survey as an alternative dimension for assessment of quality of life in this trial, hypothesizing that it might be more responsive to the intervention and improvement in the target symptoms. This decision was based on other cross sectional data from a recently completed study of breast cancer survivors (12). Furthermore, we concluded that a measure of symptoms would be essential for evaluation of the efficacy of the intervention in achieving its primary goal (relief of the target menopausal symptoms). Increasing evidence that condition specific measures are more appropriate for measuring outcomes in clinical trials supported this decision (6,7,44). Thus, the two primary outcomes for this study focus on a condition specific measure (a composite scale of menopausal symptoms) and a generic dimension of health-related quality of life (vitality).

We performed a power calculation incorporating a Bonferroni adjustment to account for two primary outcomes. This suggested that a sample of 36 per group would provide in excess of 80% power to detect as significant an effect size of 0.75 standard deviations. Such an effect size implies that the mean outcome in the intervention arm would fall at roughly the 77.3 percentile of the distribution of outcome scores in the control arm. Given the highly symptomatic nature of the women we had recruited to the study, we believed it was reasonable to expect such a large effect size in the final sample.

All statistical analyses were performed on an intent-to-treat basis (with the exception of the non-compliance analysis, described below). Univariate analyses were performed to determine the relationship of various medical, demographic and scale data to the two main outcome variables; chi-square tests were used for categorical variables, and t-tests were used for continuous variables. Multivariable analyses to determine the presence of a group effect were performed on each main outcome and the secondary outcome using analysis of covariance (ANCOVA) models, where the dependent variables were 1) the change between a woman's baseline and follow-up outcome score or 2) the woman's follow-up outcome score. The change score and follow-up models were adjusted for age, current tamoxifen use, prior chemotherapy, ethnicity (white vs. non-white), partnered (vs. non-partnered), and RAND physical and mental health composite scores. For the vitality outcome, analyses were also adjusted for use of the hot flash medication clonidine, which can cause drowsiness.

Additional analyses were performed to assess the efficacy of the intervention while accounting for non-compliance. We applied the method of Angrist, Imbens, and Rubin (45), which estimates the average causal effect of intervention among those who would comply with the treatment. The underlying statistical approach treats the control arm as a mixture of individuals who would comply with the intervention if assigned and individuals who would not comply, with the comparison of interest based on differences in the distributions of outcomes among intervention-arm compliers and control-arm compliers. In this method, data

from the intervention arm provides information on the fraction of subjects in the control arm expected to be compliers. The compliance analyses were not multiply adjusted.

RESULTS

Subjects

Between January 31, 1996 and September 23, 1998 we entered 76 eligible women into the randomized trial. Recruitment of women for this trial was substantially more difficult than was anticipated. Figure 1 shows the flow of participants from screening and eligibility, through randomization, treatment, and completion of the study. We screened 197 women by telephone who met the minimum eligibility with regard to breast cancer diagnosis (free of cancer and at least eight months and no more than five years after the diagnosis of stage I or stage II breast cancer). Among these women, 98 (50%) were deemed ineligible, with the most common reasons being inadequate severity of target symptoms (35%), refusal to consider a pharmacological agent for relief of symptoms (33%), being medically ineligible (serious medical conditions, diagnosed more than 5 years earlier, on ERT, not menopausal) (18%), and the remainder for a variety of other reasons. We screened 99 potential participants who came for an in-person visit with the study nurse practitioner. After a more thorough assessment of the target symptoms and eligibility for the study, an additional 23 women were excluded for the following primary reasons: current symptoms of a major depression (35%), target symptoms were too mild (26%), and the remainder for a variety of other reasons including poor compliance with data collection, medically ineligible, transportation problems, and being too busy to participate in a research study. Ultimately, 76 women were randomized with 39 assigned to usual care and 37 assigned to intervention. There were four dropouts during the course of the follow-up (no follow-up data collected) and all occurred in the intervention condition: 2 were because of a family member's illness and 2 women became medically ineligible because of the development of metastatic disease, leaving a final sample of 39 women in usual care and 33 women in intervention. A post-hoc power calculation confirmed

that comparing groups of size 39 and 33 would provide in excess of 80% power for detecting a difference of 0.75 standard deviations in each of the primary outcomes at the 0.025 significance level.

The medical and demographic characteristics of the 72 women who participated in this study and were evaluable are shown in Table 1. On average, these women were 54.5 years old and were 2.5 years since the time of their breast cancer diagnosis. They had been postmenopausal for about 7 years and about 57% of them had taken hormone replacement in the past. The majority of the women were married, well educated, and affluent, being demographically similar to other samples of breast cancer patients we have studied, with the exception of being 90% white. Two thirds of the women had received a lumpectomy with radiation as their primary treatment, and 56% of them were on tamoxifen at the time they entered this study. The treatment and usual care groups were balanced on all factors with the exception of race/ethnicity, where by chance more of the non-white participants were assigned to the treatment condition.

Symptoms and Quality of Life Prior to Randomization

In Table 2 we present results from the instruments used for the outcome assessments in this trial. Overall, these women exhibited high levels of functioning and quality of life, comparable to what we have seen in other samples of breast cancer survivors (12,36). The scores on the RAND 36-item health survey are at or above the mean for the general population of healthy women (46), which is confirmed by the Composite Physical and Mental Health Scales that are nearly 50, which is the median score for the general population. The two study groups scored similarly on all of the RAND scales with the exception of the Vitality scale, for which the usual care group had a significantly lower baseline score ($p=0.05$).

Relationship between Symptoms and Quality of Life

The women who participated in this study were highly symptomatic with respect to the target menopausal symptoms. Twenty-seven of the 72 (38%) had all three target menopausal symptoms (see Figure 2). An additional 32 of the 72 (44%) had two of the three target menopausal symptoms. Only 18% had a

single target symptom. Overall, hot flashes were the most common target symptom (97% of study participants) followed by vaginal dryness (71%) and urinary incontinence (51%). The mean severity score for each symptom (hot flashes, vaginal symptoms, urinary symptoms), as well as the composite symptom scale score are shown in Table 2. In addition to being the most prevalent symptom, hot flashes were rated as the most severe (2.6 on a scale of 0 to 4) in both the intervention and usual care groups. Although the severity of urinary symptoms was significantly worse in the usual care group, the composite symptom scale score was not significantly different between the two study groups.

At baseline, in spite of having moderate to severe menopausal symptoms, these breast cancer survivors reported normal quality of life on a standardized generic measure of health-related quality of life (Table 2). Sexual functioning was the only summary scale on the CARES to demonstrate moderate problems. To explore the relationship between symptoms and quality of life, we constructed a correlation matrix to examine the individual symptom scales and the composite symptom scale in relationship to the generic (RAND 36-item health survey) and cancer-specific quality of life (CARES) instruments. The hot flash scale was not correlated significantly with any of the RAND or CARES scales. The urinary symptom scale was weakly correlated with only the Vitality Scale with $R = -0.24$ ($p=0.045$). The vaginal symptom scale was correlated with the CARES Global, Marital and Sexual summary scales, but these correlations were weak to moderate in strength (range 0.236 to 0.500). The composite symptom scale (hot flashes, urinary symptoms, and vaginal symptoms) did not have a significant relationship to any of the RAND scales. However, it was modestly correlated with the CARES Global, Psychosocial, and Sexual summary scales (range 0.281 to 0.417).

Assessing the Effects of the CMA Intervention Program

We had two pre-specified primary endpoints (the composite menopausal symptom scale and the RAND Vitality scale), as well as one exploratory secondary endpoint (sexual functioning). Table 3 presents the results of the crude and adjusted change scores in the intervention group compared to the control group.

We found a highly significant difference between groups in the change scores for the symptom scale (p=0.0004), with women the intervention group reducing the severity of their menopausal symptoms over time significantly more than the women in the usual care group. We also analyzed these data by examining the follow-up score in each group, adjusted for baseline covariates. As illustrated in Figure 3, the intervention group reported a significantly greater decrease in the composite symptom scale score at follow-up than the usual care group (p=0.001).

For the Vitality Scale outcome, both the crude and adjusted change score analysis (Table 3) showed no difference between groups (p=0.77); follow-up scores, adjusted for baseline covariates, also revealed the same result (p=0.27) (see Figure 4). Since the evaluation of vitality could be complicated by the use of the sedating drug clonidine, we explored whether controlling for this would change the analysis (58% of the women in the intervention group took clonidine for at least part of the 4 month study period). Both analyses still showed no difference between groups (p=0.40 for the change score analysis, and p=0.13 for the follow-up group score analysis).

For the secondary outcome, sexual functioning, we detected a significant difference in change scores between the two groups (Table 3). After adjustment for covariates, the intervention group improved significantly more between baseline and follow-up than the usual care group (p=0.04). This result was mirrored in the follow-up score analysis, with the intervention group having significantly better sexual functioning at follow-up than the usual care group (Figure 5, p=0.01).

To have a better understanding of what aspects of sexual functioning the intervention might have influenced, we examined the eight individual items of the CARES Sexual Summary scale in an exploratory analysis. For women in the usual care group, only two items improved significantly over the four months of the study, and these included the items related to arousal and orgasm. In contrast, the women in the intervention group demonstrated significant improvement in all 8 items of the CARES Sexual Summary Scale

(sexual attractiveness for self and partner, interest in sex for self and partner, increase in frequency of sex, arousal, lubrication and orgasm).

Nine of the women in the intervention group (27%) refused medications at some point during the study. The refusal rate was highest among those being treated for hot flashes; 32% of them refused to take at least one of the medications suggested by the nurse practitioner. Only two women (6%) refused treatment for vaginal dryness, and none of the women refused treatment for urinary incontinence. The results of the non-compliance analyses mirrored the results of the intent-to-treat analyses, both for the change score analyses and the follow-up score analyses. For the change score analysis, there was a highly significant group difference in symptom scores ($p<0.0001$), no group difference in vitality ($p=0.73$) and a significant difference in sexual functioning ($p=0.03$). The follow-up group score analysis results were also similar, again with a very significant group difference in symptom scores ($p=0.0001$) and sexual functioning ($p=0.02$). The group difference in follow-up scores for vitality was borderline significant ($p=0.07$), consistent with the significant baseline difference in vitality noted earlier and the finding of no significant change score from baseline to follow-up noted just above.

We also examined treatments used by the women in the usual care group during the four months on-study. Of the 39 women in the control group, 26% of them started vitamin therapy, 3% began a traditional or folk remedy, 13% began using a special diet, and 26% began using mind body techniques. As can be seen, in their quest for control of symptoms, these highly symptomatic women frequently adopted these alternative remedies. In addition, 4 women in the usual care group received either prescription or over the counter medications to address their symptoms (1 each used estrogen cream, a belladonna preparation, Replens, and gynelotromin).

DISCUSSION

We developed and evaluated a comprehensive assessment and management program for breast cancer survivors experiencing multiple and severe menopausal symptoms. The intervention applied existing methods of education, counseling and non-estrogen containing pharmacological therapies tailored to the needs and preferences of the symptomatic woman. Not only was the intervention feasible, but it also resulted in significant improvement in menopausal symptoms with a secondary finding of improved sexual functioning. However, vitality--an important general dimension of health related quality of life—was not improved by the intervention.

There are a number of strengths and limitations of this study. The randomized design and detailed assessment of the baseline and follow-up status of the participants allow us to have confidence in the results. The comprehensive evaluation of medical, demographic and quality of life factors enabled us to control for relevant covariates. Nevertheless, the homogeneous nature of the sample (women with moderate to severe symptoms) makes it difficult to generalize about the benefits of this type of intervention in less symptomatic women. Overall, we observed that the breast cancer survivors in this study were very reluctant to try currently recommended conventional non-estrogen alternatives for the control of their hot flashes. Interestingly, many of the same women who were reluctant to try conventional pharmacological agents for the control of menopausal symptoms had tried or expressed a willingness to try alternative therapies, particularly herbal or dietary supplements. Most patients were unaware of the lack of information regarding the safety and effectiveness of these therapies.

We had anticipated that menopausal symptoms would have important effects on quality of life. In particular, we had hypothesized a measurable impact on vitality. In the results of the correlation among symptoms and quality of life scales summarized earlier, only vaginal dryness had any significant relationship to the quality of life dimensions that were measured. Further, correlations among symptoms and quality of

life scales were significant only for several dimensions of the CARES scale. The composite symptom scale did not have a significant relationship with any of the RAND quality of life scales, but it was modestly correlated with several CARES scales. To some extent, the larger number of questions on the CARES explains these relationships (139 on the CARES versus 36 on the RAND), as well as the marital and sexual dimensions that are only assessed on the CARES. Nevertheless, it is possible that while symptoms may be bothersome, they may not be substantial enough to affect the major dimensions of health-related quality of life (e.g., physical or emotional well-being). In the recently completed Breast Cancer Prevention Trial (7), although participants treated with tamoxifen had significantly higher rates of hot flashes, sweats and vaginal discharge compared to those taking placebo, there was no measurable impact on quality of life as measured by the MOS SF-36 (6). The failure to measure a significant improvement in quality of life as assessed by the Vitality Scale undoubtedly relates to its limited correlation with symptoms. In addition, the use of clonidine as one of the treatment regimens for hot flashes could have confounded a measured benefit. Further, the relatively small sample size for the study may have prevented the detection of a very small effect on this component of quality of life.

We have previously studied the predictors of sexual health in two large samples of breast cancer survivors (47) and in healthy postmenopausal women (48). In both of those studies, we found that the most important and consistent predictors of sexual health were the presence or absence of vaginal dryness, emotional well-being, the quality of the partnered relationship, and whether or not the woman's partner has sexual problems (47,48). Vaginal dryness was one of the strongest predictors of sexual dysfunction in both breast cancer survivors and postmenopausal women. As a result of those findings, we have previously recommended the evaluation of clinical interventions targeting vaginal dryness as an important strategy for dealing with sexual dysfunction in breast cancer survivors (47). Therefore, we were encouraged to find that our CMA intervention demonstrated improvement in sexual functioning. The symptom of vaginal dryness

was targeted specifically by the CMA intervention, whether or not a woman was sexually active, and other sexual concerns were addressed by the nurse practitioner in the course of psychosocial evaluation. Thus, patients with sexual problems were not only managed with lubricants and vaginal moisturizers, but also with information and referral to self-help or professional resources. Perhaps, this comprehensive approach contributed to the improvement we saw in this area. The mechanism of improved overall sexual functioning as a result of our intervention is uncertain. One possibility is that enhanced anatomical competence (e.g., more optimal vaginal lubrication during sex) leads to several positive outcomes beyond simply improved comfort. For example, it is plausible that women perceive better arousal and stimulation owing to improved secretions during sex, which enhances sexual function in a more global manner.

Finally, it is important to ask how this intervention might be incorporated into clinical practice. Increasingly, medical practice has been focusing on women's health issues, with counseling related to menopause being an important area of interest. Since most breast cancer survivors will be unwilling to consider hormone replacement therapy with estrogen containing regimens (49,50), existing clinical programs that counsel regarding the use of estrogen will not be appropriate. However, clinicians counseling women with a history of breast cancer can adopt the comprehensive assessment and management strategies used in this intervention. Under these circumstances, one can achieve significant symptom control and may improve sexual functioning. As the number of breast cancer survivors is expected to increase in the coming years, this clinical problem will become more common, especially in women's health clinics and oncology practices that care for this population. We can no longer say to these women there is nothing that can be done. It is our obligation to address their symptoms and concerns through use of a comprehensive assessment and management strategy.

FIGURE LEGENDS

Figure 1: Study recruitment flow chart.

Figure 2: Venn diagram showing individual menopausal symptoms (hot flashes, vaginal dryness, urinary incontinence) and their overlap in the study sample.

Figure 3: Change in symptom scale score from baseline to follow-up, adjusted for covariates, in the intervention and usual care groups ($p=0.001$). A lower score indicates a lesser severity of symptoms.

Figure 4: Change in Vitality Scale score from baseline to follow-up, adjusted for covariates, in the intervention and usual care groups ($p=0.07$). A higher score indicates greater energy/vitality.

Figure 5: Change in CARES Sexual Functioning Summary Score from baseline to follow-up, adjusted for covariates, in the intervention and usual care groups ($p=0.01$). A lower score indicates a lesser severity of problems.

ACKNOWLEDGMENTS

We wish to thank the women with breast cancer who participated in this study. In addition, the authors thank the Iris Cantor-UCLA Women's Center and Center of Excellence in Women's Health for their support of this project.

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Table 1: Baseline Medical/Demographic Characteristics N=72 Women
Means (Standard Deviations) for Continuous Variables and
Frequencies (Percentages) for Categorical Variables

	Usual Care Group	Intervention Group	All Women	p-value[1]
Age	54.5 (5.5)	54.6 (6.4)	54.5 (5.9)	.91
Yrs Since Dx	2.6 (1.4)	2.4 (1.3)	2.5 (1.3)	.50
Years Since LMP[2]	7.2 (7.7)	6.5 (6.8)	6.9 (7.3)	.67
Ever Taken HRT[3]	23 (59%)	18 (55%)	41 (57%)	
Ethnicity				
Asian	0 (0%)	1 (3%)	1 (1.5%)	
Black	1 (3%)	4 (12%)	5 (7%)	.026
Hispanic	0 (0%)	1 (3%)	1 (1.5%)	(white vs.
White	38 (97%)	27 (82%)	65 (90%)	non-white)
Marital Status				
Married	32 (82%)	27 (82%)	59 (82%)	.980
Not Married	7 (18%)	6 (18%)	13 (18%)	
Education				
Less Than College	16 (41%)	13 (39%)	29 (40%)	
College Grad	13 (33%)	13 (39%)	26 (36%)	.843
Advanced Degree	10 (26%)	7 (21%)	17 (24%)	
Employment				
Employed Full-time	21 (54%)	18 (55%)	39 (54%)	
Employed Part-time	7 (18%)	9 (27%)	16 (22%)	.482
Not Employed	11 (28%)	6 (18%)	17 (23%)	
Income				
<$45,000/year	10 (26%)	7 (21%)	17 (23%)	
$45,000-$75,000/year	11 (28%)	10 (30%)	21 (29%)	.907
>$75,000/year	18 (46%)	16 (48%)	34 (47%)	
Type of Surgery				
Lumpectomy	25 (66%)	22 (67%)	47 (66%)	.938
Mastectomy	13 (34%)	11 (33%)	24 (34%)	

[1] T-tests for continuous variables, chi-square tests for categorical variables
[2] LMP=last menstrual period
[3] HRT=hormone replacement therapy

Table 1 Continued

Cancer Treatments							
Tamoxifen use	24	(62%)	16	(48%)	40	(56%)	.267
Prior Radiation	24	(62%)	26	(79%)	50	(69%)	.113
Prior Chemotherapy	18	(46%)	16	(48%)	34	(47%)	.844
Medical Conditions							
Arthritis	11	(28%)	10	(30%)	21	(29%)	.845
Heart Disease	0	(0%)	1	(1%)	1	(1%)	n/a
Hypertension	4	(10%)	5	(15%)	9	(12.5%)	n/a
Diabetes	0	(0%)	0	(0%)	0	(0%)	n/a
Psych difficulties	2	(5%)	4	(12%)	6	(8%)	n/a
Alcohol problems	0	(0%)	0	(0%)	0	(0%)	n/a
Drug problems	0	(0%)	0	(0%)	0	(0%)	n/a
Other conditions[4]	9	(23%)	6	(18%)	15	(20%)	.610

[4] These include: osteoporosis, fibromyalgia, hypothyroidism, asthma, allergic rhinitis, ileostomy, mitral valve prolapse, ulcer, and chronic canker sores

Table 2: Baseline Scale Values for N=72 Women
Means (Standard Deviations)*

	Usual Care Group (n=39)	Intervention Group (n=33)	All Women (n=72)	p-value
Symptom Scores				
Hot flashes	2.63(1.1)	2.57(1.2)	2.60 (1.12)	.84
Vaginal	1.06(0.9)	1.08(1.1)	1.07 (1.01)	.93
Urinary	0.76(1.0)	0.39(0.5)	0.59 (0.82)	.05
Symptom scale score	**1.42(0.56)**	**1.31(0.62)**	**1.37(0.59)**	**.44**
RAND 36-item Health Survey				
Physical Functioning	84.9(14.6)	85.6(18.5)	85.2(16.4)	.85
Role Limits - Physical	85.9(24.2)	83.3(29.1)	84.7(26.4)	.68
Role Limits - Emotional	76.9(31.7)	81.8(35.4)	79.2(33.3)	.54
Vitality	**56.7(22.2)**	**66.5(20.3)**	**61.2(21.7)**	**.05**
Emotional Well-being	76.3(12.0)	79.4(15.2)	77.7(13.5)	.34
Social Functioning	85.6(16.6)	89.4(19.3)	87.3(17.9)	.37
Pain	81.1(20.1)	80.6(19.3)	80.9(19.6)	.92
General Health	77.4(17.2)	80.6(17.9)	78.9(17.4)	.45
Composite Scales				
Physical	52.0(6.8)	51.6(7.4)	51.8(7.0)	.83
Mental	49.1(7.8)	52.1(9.5)	50.5(8.7)	.14
CARES Scores				
Global	0.55(0.32)	0.51(0.40)	0.53(0.36)	.68
Physical	0.40(0.42)	0.41(0.42)	0.40(0.46)	.91
Psychosocial	0.61(0.39)	0.63(0.54)	0.62(0.90)	.86
Marital	0.43(0.49)	0.26(0.35)	0.35(0.44)	.07
Sexual	**1.36(0.91)**	**1.26(0.91)**	**1.32(0.90)**	**.64**
Medical Interaction	0.33(0.45)	0.18(0.35)	0.26(0.42)	.15

*Scales indicated in bold are the primary and secondary outcomes for the study

Table 3: Crude and Adjusted Change Score Analyses for Primary and Secondary Outcomes[1]

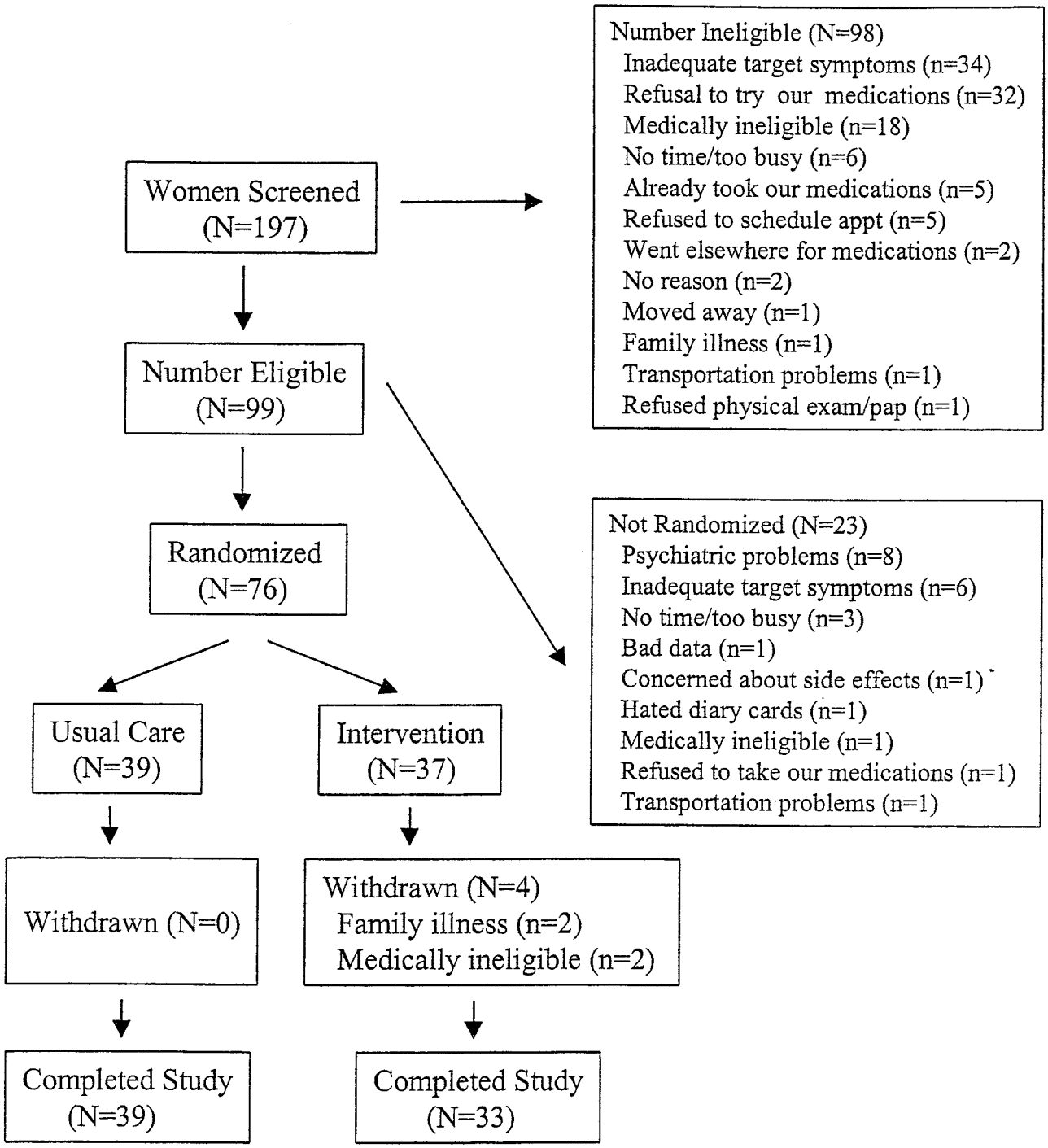
	Intervention Group	Usual Care Group	P-value for group difference
Symptom Score*			
Unadjusted Mean Change Score	0.57	0.09	0.0000
Adjusted Mean Change Score	0.61	0.19	0.0004
RAND Vitality Scale**			
Unadjusted Mean Change Score	0.8	2.3	0.72
Adjusted Mean Change Score	3.0	4.3	0.77
Adjusted Mean Change Score, including clonidine use as a covariate	4.1	-0.5	0.40
CARES Sexual Functioning Scale***			
Unadjusted Mean Change Score	0.46	0.11	0.03
Adjusted Mean Change Score	0.38	-0.015	0.04

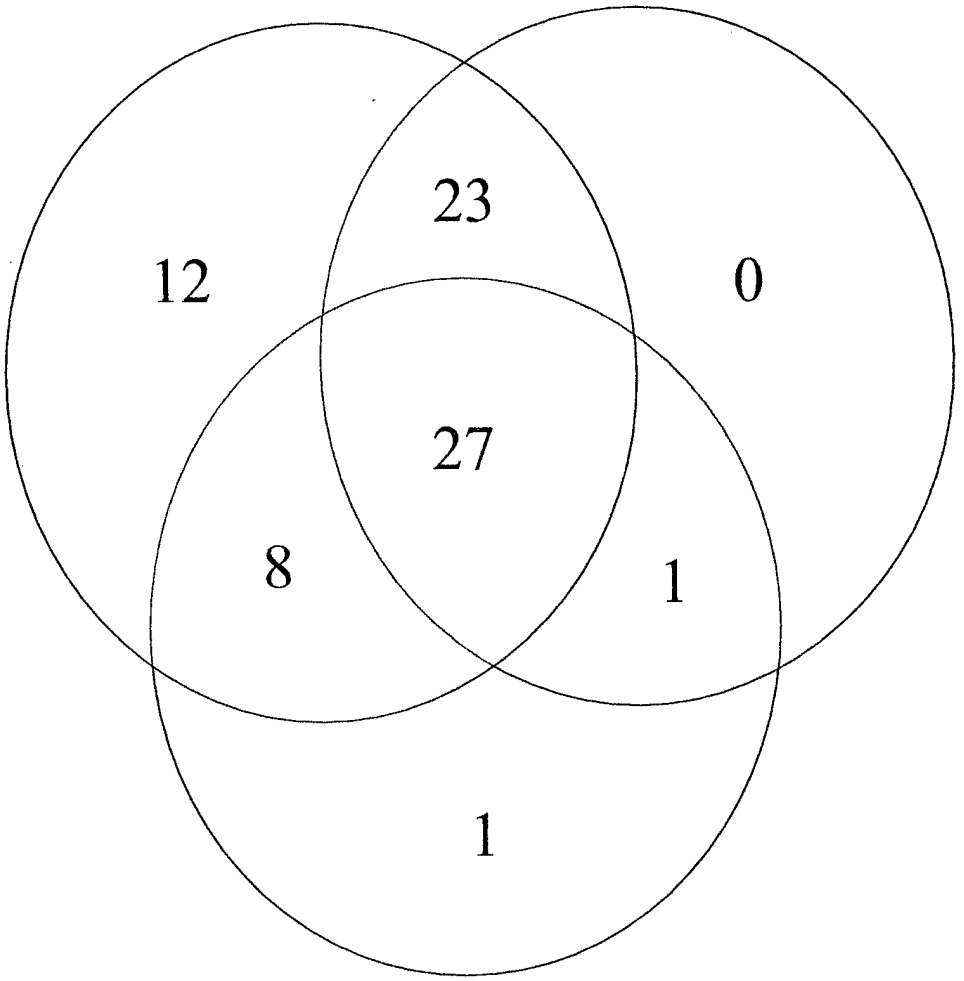
1. Adjusted for the following covariates: age, current tamoxifen use, prior chemotherapy, race (white vs. other), marital status (partnered vs. other), and RAND Mental and Physical Composite Scores. A positive change score indicates improvement over time, while a negative change indicates worsening.

*7-item symptom scale that measures how bothered a woman is by each of 7 symptoms (2 about vasomotor symptoms, 3 about vaginal dryness, 2 about urinary incontinence). The scale score is a mean of the ratings on each of the 7 items, and ranges from 0= "not at all" to 4= "extremely."

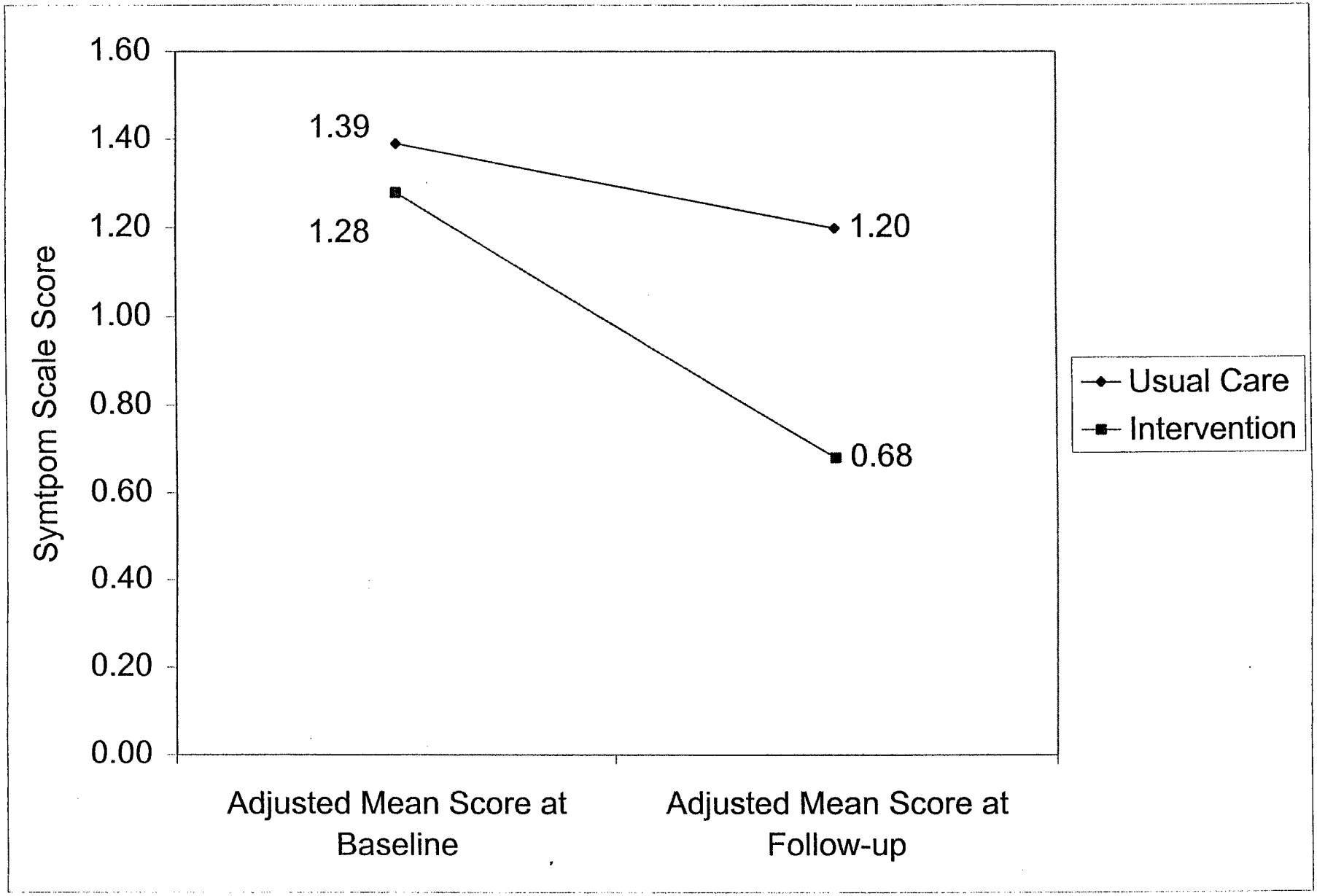
** The RAND vitality scale is scored between 0 and 100 with 0 = complete lack of energy to 100 = full of energy.

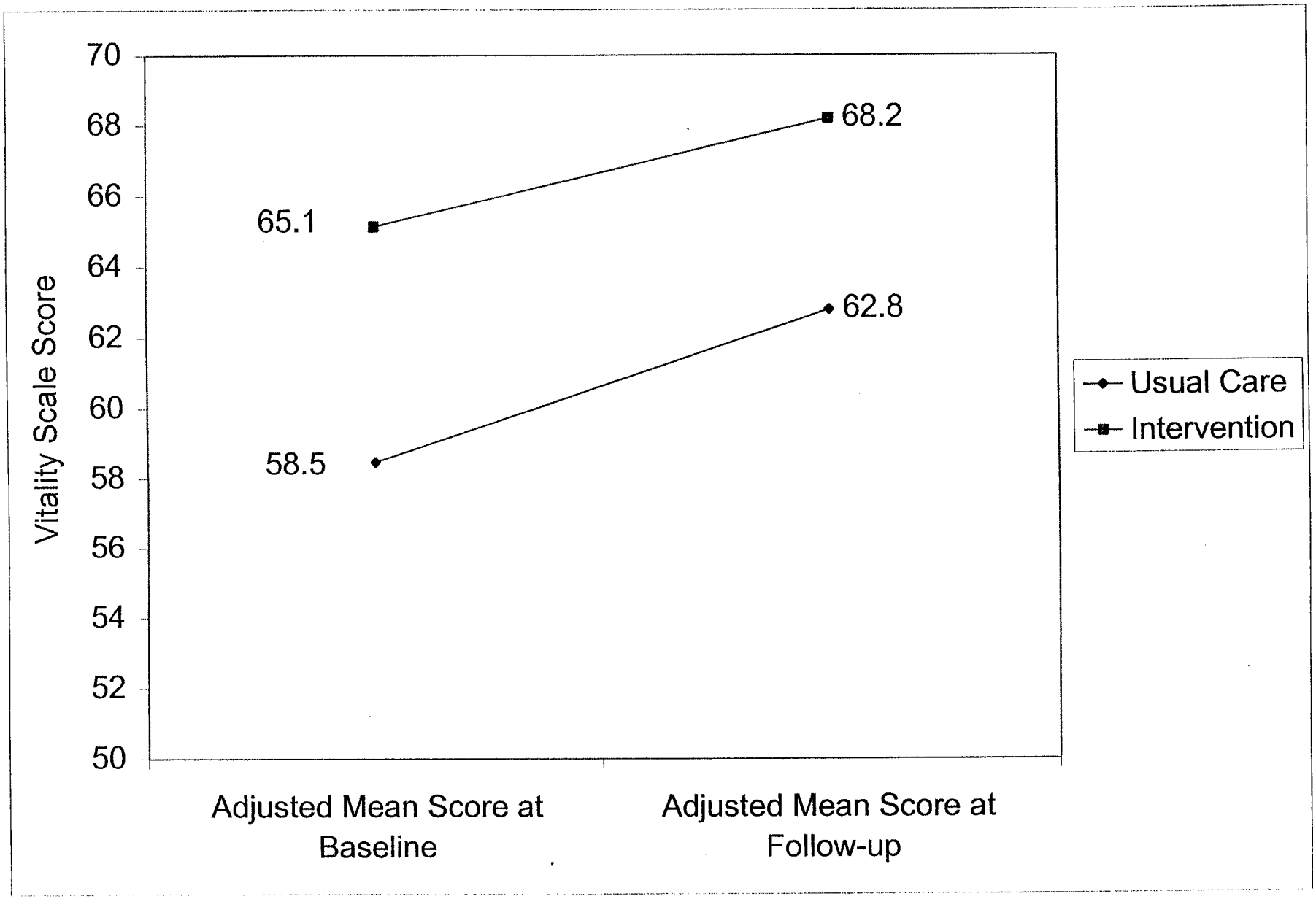
*** The CARES Sexual Functioning Scale measures problems with sexual interest and sexual dysfunction. A hig score indicates more problems, with 0 = no problems and 4 = very much a problem.

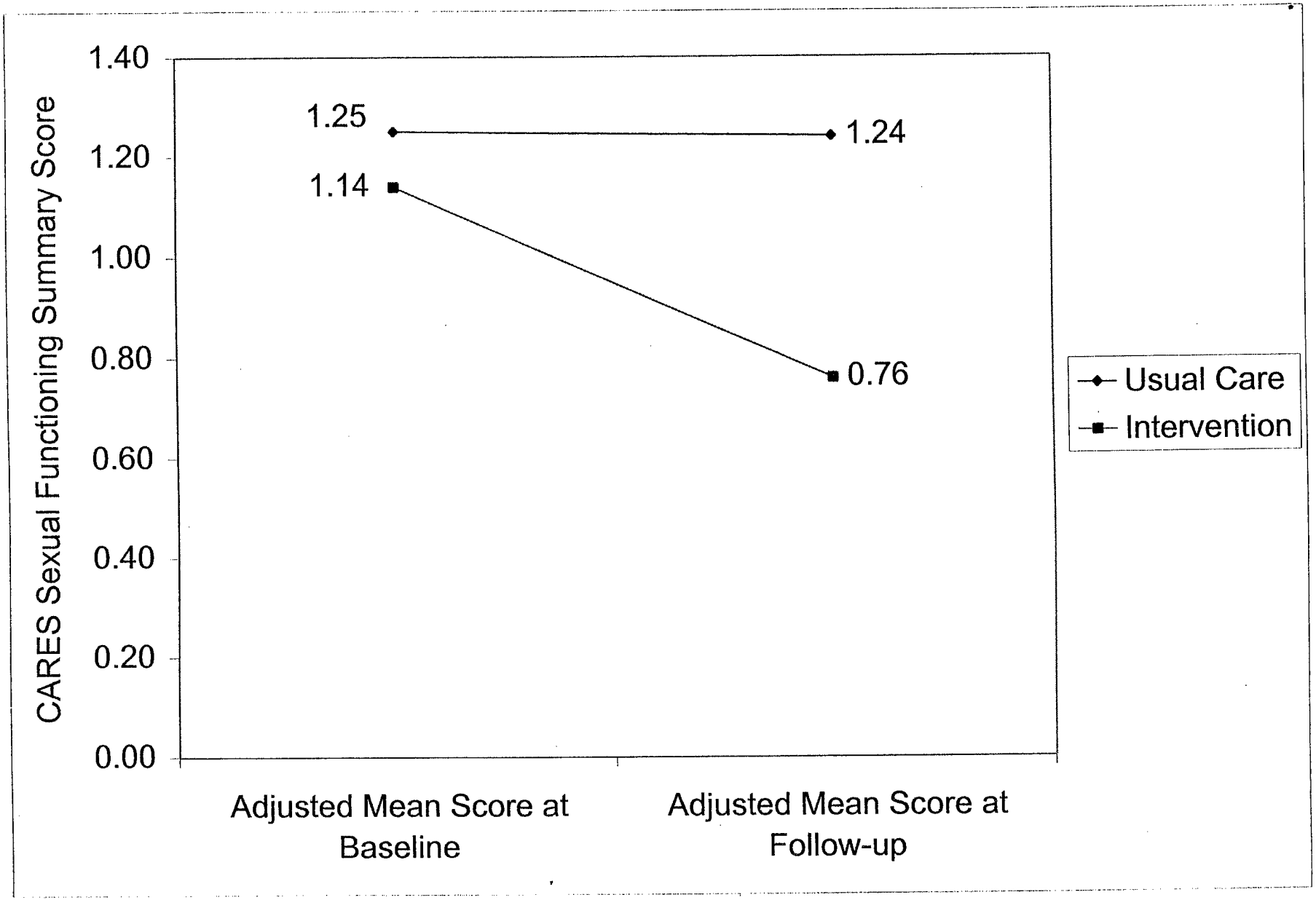

Women Screened (N=197)
Number Ineligible (N=98)
Inadequate target symptoms (n=34)
Refusal to try our medications (n=32)
Medically ineligible (n=18)
No time/too busy (n=6)
Already took our medications (n=5)
Refused to schedule appt (n=5)
Went elsewhere for medications (n=2)
No reason (n=2)
Moved away (n=1)
Family illness (n=1)
Transportation problems (n=1)
Refused physical exam/pap (n=1)
Number Eligible (N=99)
Not Randomized (N=23)
Psychiatric problems (n=8)
Inadequate target symptoms (n=6)
No time/too busy (n=3)
Bad data (n=1)
Concerned about side effects (n=1)
Hated diary cards (n=1)
Medically ineligible (n=1)
Refused to take our medications (n=1)
Transportation problems (n=1)
Randomized (N=76)
Usual Care (N=39)
Intervention (N=37)
Withdrawn (N=0)
Withdrawn (N=4)
Family illness (n=2)
Medically ineligible (n=2)
Completed Study (N=39)
Completed Study (N=33)



N=72 women in the study


1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Symtpom Scale Score
1.39
1.28
1.20
0.68
Usual Care
Intervention
Adjusted Mean Score at Baseline
Adjusted Mean Score at Follow-up


70
68
66
64
62
60
58
56
54
52
50
Vitality Scale Score
65.1
68.2
58.5
62.8
Usual Care
Intervention
Adjusted Mean Score at Baseline
Adjusted Mean Score at Follow-up


1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
CARES Sexual Functioning Summary Score
1.25
1.24
1.14
0.76
Usual Care
Intervention
Adjusted Mean Score at Baseline
Adjusted Mean Score at Follow-up

CLIMACTERIC 1999;2:1–8

APPENDIX 2

Development and validation of a physical examination scale to assess vaginal atrophy and inflammation

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Key words: ATROPHY, INFLAMMATION, MENOPAUSE, VAGINAL, GENITAL, SCALE

ABSTRACT

Background The assessment of vaginal atrophy is central to menopause-related research and clinical practice. However, methods of grading vaginal atrophy have not been subjected to reliability and validity assessments.

Objective To assess the validity and reproducibility of selected vaginal examination findings proposed to represent vaginal atrophy and inflammation.

Design Cross-sectional study.

Participants A convenience sample of 40 postmenopausal volunteers with past history of breast cancer.

Measurements Participants completed questionnaires to assess vaginal symptoms. Pelvic examinations were carried out using specified criteria to assess the vaginal appearance. Vaginal cytological smears and pH measurements were performed using standardized techniques.

Results A four-item physical examination atrophy scale had an α reliability of 0.48 and was statistically significantly correlated with pH ($r = 0.55$) and parabasal cells ($r = 0.50$). A three-item physical examination inflammation scale had an α reliability of 0.48. It was not significantly associated with vaginal smear-measured inflammation. Masked inter-rater agreement for the examination was 90%. Self-reported symptoms of itching/irritation or dryness were poorly related to findings on physical examination.

Conclusions These results offer objective validation that the physical characteristics proposed to represent atrophy are related to biomarkers of this condition. A relationship between examination characteristics believed to represent inflammation and inflammation biomarkers was not upheld.

INTRODUCTION

Vaginal atrophy is widely recognized as one the major problems of the postmenopause[1]. However, the absence of a universal terminology and standardized methods of measurement limit our understanding of the natural history of vaginal atrophy and its response to various interventions.

The term 'atrophic vaginitis', although commonly utilized, remains imprecisely defined. It is

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ORIGINAL ARTICLE

Received 22–12–98
Revised 15–06–99
Accepted 16–06–99

A3424:AMA:First Proof: 29 July 1999 Paper:C98/33A

used clinically to refer to several conditions: atrophic signs on physical examination; cytologically determined atrophy; and the presence of vaginal symptoms such as irritation or dyspareunia (with or without apparent signs of atrophy on examination).

Early methods of assessing vaginal atrophy did not specify the criteria by which the physical examination was categorized into mild, moderate or severe degrees of atrophy[2]. While subsequent vaginal atrophy grading systems provided descriptive categories that were judged to determine atrophy, the response categories remained relatively non-specific[3,4]. For example, in the Vaginal Health Index[4], overall vaginal elasticity is rated as 'none, poor, fair, good or excellent', a relatively broad response set which could be interpreted differently by individual raters. More importantly, the validity of vaginal physical examination methods to assess atrophy has not been assessed. In addition, discrimination between 'atrophic vaginitis' and 'vaginal atrophy' is not clear: does vaginitis infer symptoms while atrophy implies solely a physical finding?

The goals of the present study were to: propose a set of clinical examination findings that may represent vaginal atrophy or vaginal inflammation; validate the examination findings by assessing their relationships to biomarkers of atrophy or inflammation; and examine the relationship between the physical and biological markers of atrophy or inflammation and self-reported genital symptoms.

METHODS

Studies were conducted with informed consent of participants and approval of the University of California at Los Angeles (UCLA) Medical Human Subjects Protection Committee. The study was conducted in two phases. In phase I, the vaginal appearance assessment instrument was designed and piloted. During phase II, the instrument was validated.

Phase I: instrument development

Two investigators (GAG and JGO) developed the vaginal appearance instrument items (Table 1) and proposed the constructs that these items measured, based on literature review[2–6] and on clinically founded hypotheses regarding the appearance of atrophic or inflamed vaginal tissue. The exact criteria for rating each item as present or absent are given in the Appendix. The physical examination signs postulated as signifying *atrophy* were: presence of vaginal wall petechiae, friability of the vaginal wall, conization (markedly decreased elasticity), absence of rugae, flattened cervix, narrowed cervix and pale-appearing epithelium. Features proposed to represent *inflammation* were: red labia minora, red urethral meatus, bright red areas on vaginal walls and red urethral caruncle. A three-level response set for each item was initially used (for example, rugae were graded as normal, diminished or absent; elasticity was graded as normal, diminished or conization). However, after two investigators (GAG and JGO) conducted blinded, repeated, same-day pilot testing of the measures in three sets of ten participants, response categories were collapsed to each finding being present or absent, because agreement for three-level responses was low (less than 50%). Vaginal pallor was so difficult to rate reliably that it was dropped from the candidate items. These same rating criteria were used in phase II.

Table 1 Items in vaginal physical examination instrument

Proposed category+ and items	*Prevalence† (%)*
Atrophy	
Cervix narrowed	58.6
Cervix flattened	55.2
Presence of petechiae	55.0
Vaginal wall friable	27.5
Conization present	25.0
Absence of rugae	22.5
Inflammation	
Labia minora red	25.0
Urethral meatus or caruncle red	18.0
Red area vaginal walls	7.5

*Items shown by condition (atrophy or inflammation) that they were hypothesized to represent: bold items were retained in final subscale; †prevalence in phase II validation sample ($n = 40$) except for items related to cervix where $n = 29$ owing to hysterectomy in 11 women

Phase II: instrument validation

In phase II, the results of which are reported here, the vaginal examination instrument was validated by assessing its construct validity. One research Nurse Practitioner (LZ) completed the assessment in an independent sample of 40 women who were enrolled in one of two studies: a randomized clinical trial of comprehensive menopausal assessment in breast cancer survivors, and a study to assess

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the attitudes of breast cancer survivors towards hormone treatment. Participants had not been taking oral or vaginal estrogens or progestins or any other vaginal over-the-counter preparation for at least 3 months prior to study entry. Participants in phase II underwent a pelvic examination, during which the vaginal appearance assessment, pH testing and vaginal cytological collection for determination of maturation index were performed using standardized techniques. Vaginal pH was measured in the mid-lateral portion of the vagina, using Nitrazine paper (pH 4.5–7.5). Subsequently, the cytological sample for maturation index determination was taken from the mid-lateral vaginal wall using a saline-moistened cotton tip applicator. Two investigators (LZ and GAG) performed same-day serial examinations on ten additional participants to assess the inter-rater reliability of the vaginal examination.

Vaginal smear maturation indices were read by an expert cytopathologist who was unaware of the study hypotheses. Vaginal smear inflammation was rated as present if an excess of polymorphonuclear leukocytes or cells manifesting morphological features consistent with inflammation were present on the smear[7]. Inflammation was considered present if these characteristics were present anywhere on the smear (i.e. either vaginal or cervical cells). Participants also completed a self-report symptom check-list that assessed the presence of selected gynecological symptoms (vaginal dryness or vaginal itching/irritation) within the past 2 weeks.

Scale creation was done as follows. First, the examination items were specified a priori as possibly representing atrophy (six items) or inflammation (three items) (listed in Table 1). Next, based on the data gathered in phase II, the correlation of each item with the remaining items in the proposed subscale (atrophy or inflammation) was tested. To determine internal consistency, Cronbach's α was calculated for the atrophy and inflammation scales.

Of those items initially postulated to represent atrophy (conization, absence of rugae, presence of petechiae, friability of the vaginal wall, narrowed cervical width and flattened cervical height), all were retained in the vaginal atrophy subscale on the basis of this correlation analysis. Cronbach's α for the full atrophy scale was 0.71. However, because 11 participants in the sample had undergone hysterectomy, the sample size for assessing the relationships between the atrophy scale and the clinical and biological data would have been markedly reduced had all six items been used. Therefore, for this analysis, only four atrophy items were used (bold in Table 1), those that were available for all 40 women. The α reliability of the four-item atrophy scale was 0.48. All proposed items remained in the inflammation subscale (red labia minora, red areas on vaginal walls and either redness of the urethral meatus or a red urethral caruncle). The α reliability of the inflammation subscale was 0.48.

Each participant was then given a summary score of between 0 and 4 for atrophy and 0 and 3 for inflammation. To assess construct validity, correlations were calculated to determine whether the atrophy and inflammation scales were related to other known biological measures of atrophy (maturation index) and inflammation (inflammation on cytological reading) or to self-reported symptoms of vaginal dryness or itching/irritation. A weighted average of the maturation index was also constructed, giving one point to parabasal cells, two points to intermediate cells and three points to superficial cells (thus, higher scores indicate more mature epithelium). The correlation of this weighted maturation score with the atrophy and inflammation subscales and with self-reported symptoms was assessed. Because the data were not normally distributed, all correlations were done using Spearman's rank correlation coefficient. In addition, alternative forms of weighting the maturation index were applied to evaluate the effect of weighting on the strength of the observed correlations. All analyses were done using Statistical Analysis System (SAS) software[8].

RESULTS

The average age of the 40 women in the phase II sample was 57.9 years (range 41–79 years). Most were white (92%), the majority were married (67%) and 43% had a college or more advanced degree. The mean duration since breast cancer diagnosis was 2.8 years (range 0.6–5.6 years). Eleven women (28%) had undergone a hysterectomy and bilateral oophorectomy (one for carcinoma *in situ* of the cervix, the remainder for benign diseases). All were postmenopausal.

The physical examination characteristics initially proposed to represent vaginal atrophy and inflammation are reproduced in Table 1. Highlighted in bold are the items constituting the atrophy and inflammation subscales. Note that although the cervical characteristics were well correlated with the remaining items (see 'Methods'), for this analysis they were not included in the atrophy subscale, to maximize the

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sample size for the remaining correlational analyses with symptoms and biomarkers. The prevalence of each of the examination findings in the validation sample is also given, demonstrating variation in the items sufficient to allow estimates of correlations.

Table 2 Inflammation and atrophy scores, biological characteristics and self-reported vaginal symptoms of participants

Characteristics	*Mean*	*Range*
Physical examination		
Atrophy score*	1.30	(0–4.0)
Inflammation score†	0.50	(0–3.0)
Biomarkers		
Parabasal cells	46.68	(0–100)
Intermediate cells	46.66	(0–100)
Superficial cells	6.66	(0–40)
Maturation score‡	159.97	(100–240)
Vaginal pH	6.30	(4.5–7.5)
Cytological inflammation (%)	17.5	
Self-reported symptoms		
Vaginal dryness (% yes)	55.0	
Vaginal itching/irritation (% yes)	25.6	

*Atrophy score: conization, absent rugae, petechiae present, friable vaginal wall (1 point each); †inflammation score: red labia minora, any bright red area vaginal walls, red urethral meatus or red caruncle (1 point each); ‡maturation score calculated as weighted average: (1 × parabasal) + (2 × intermediate) + (3 × superficial)

Formula for maturation score expressed correctly?

Six of the seven items in the instrument (three atrophy and three inflammation) were assessed for inter-rater agreement, because one of the atrophy items (friability to smear) was performed only by the second examiner. The overall agreement for all six items was 90%. The agreement for specific items ranged from 83% (red labia minora and petechiae present) to 100% (conization).

Atrophy and inflammation subscale scores, biological characteristics and clinical symptoms of the phase II sample are given in Table 2. The mean vaginal examination atrophy score was relatively low, at 1.3 (maximum value 4). In contrast to the low prevalence of atrophy by physical examination, cytologically defined atrophy was common: maturation indices rarely included superficial cells, and parabasal cells were present 47% of the time, on average. Vaginal examination inflammation scores were low, with a mean value of 0.5 (maximum value 3) (Table 2). Inflammation was more frequently present by cytological reading, occurring in 17.5% of cases. Slightly over half of the sample reported vaginal dryness, and approximately a quarter endorsed vaginal itching/irritation.

Table 3 summarizes the results of the construct validity assessment, displaying the correlations between the proposed physical examination criteria for atrophy and inflammation, the biological markers for atrophy and inflammation, and the symptoms of dryness or itching/irritation. Correlations shown in bold face were statistically significant. Correlations between the atrophy

Table 3 Correlations* between vaginal examination appearance, biological characteristics and self-reported vaginal symptoms

	Intermediate	*Superficial*	*Maturation score†*	*Vaginal pH*	*Cytological inflammation*	*Atrophy score‡*	*Inflammation score§*	*Dryness*	*Itching/irritation*
Parabasal	**–0.92**	**–0.62**	**–0.98**	**0.76**	0.29	**0.50**	0.18	–0.16	–0.14
Intermediate		0.25	**0.90**	**–0.68**	–0.35	–0.45	–0.12	0.08	0.02
Superficial			**0.64**	**–0.52**	0.07	–0.50	–0.22	0.14	0.16
Maturation score				–0.77	–0.27	–0.51	–0.19	0.19	0.21
Vaginal pH					0.30	–0.55	0.29	–0.24	–0.13
Cytological inflammation						–0.15	0.06	–0.05	–0.13
Atrophy score							**0.39**	0.18	–0.01
Inflammation score								0.17	–0.23

*Spearman correlations shown in bold face are statistically significant (p values between 0.03 and 0.0001); †maturation score calculated as weighted average: (1 × parabasal) + (2 × intermediate) + (3 × superficial); ‡atrophy score: conization, absent rugae, petechiae present, friable vaginal wall (1 point each); §inflammation score: red labia minora, any bright red area vaginal walls, redness of urethral meatus or red caruncle (1 point each)

Again, please check formula for maturation score

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subscale and cytological markers of atrophy were moderately strong and statistically significant: 0.50 ($p = 0.0006$) with parabasal cells, –0.45 ($p = 0.0013$) with intermediate cells and –0.51 ($p = 0.0010$) with the maturation index summary score. The atrophy score was also significantly associated with vaginal pH, another biomarker of atrophy ($r = 0.55$, $p = 0.0003$). The examination findings proposed to represent inflammation, however, were not correlated with cytological indicators of inflammation ($r = 0.06$, $p = 0.69$).

Table 3 also illustrates discrimination between the atrophy and inflammation subscales. That is, there is no association between the atrophy score and presence of vaginal cytological smear inflammation. Conversely, the inflammation score was not correlated with any of the cytological maturity parameters. The atrophy and inflammation scores were only weakly associated with each other ($r = 0.39$, $p = 0.0123$).

Although symptoms of dryness or itching/irritation were common, they were not correlated with physical findings or biomarkers of atrophy or inflammation (Table 3). Symptoms of both dryness and itching/irritation were present in nine women. If these symptoms were considered jointly, the strength of the associations with physical examination atrophy ($r = 0.17$, $p = 0.31$) and inflammation ($r = 0.19$, $p = 0.54$) remained weak and not statistically significant.

The frequency of agreement between vaginal atrophy, defined by the presence of *any* item on the vaginal atrophy subscale (petechiae, friability, conization or absent rugae), and the presence of any of the self-reported symptoms (itching/irritation or dryness) was 62%. A χ^2 test of association for the presence of atrophy by examination and symptoms was not significant ($p = 0.28$). If the presence of any self-reported vaginal symptom is used as the criterion standard for the condition 'atrophic vaginitis', the sensitivity of the atrophy subscale examination findings for atrophic vaginitis is 78% and the specificity is 37.5%.

Similarly, agreement between vaginal inflammation, defined by the presence of any of the physical examination criteria, (red labia minora, red vaginal walls or red caruncle/meatus), and the presence of any self-reported symptom (itching/irritation or dryness) was 54%. Assessed by χ^3 test, this association was not statistically significant ($p = 0.44$). If the presence of self-reported symptoms is used as the criterion standard for the condition 'atrophic vaginitis', the sensitivity of the inflammation subscale examination findings for atrophic vaginitis is 43% and the specificity is 69%.

DISCUSSION

In this study, findings of conization, absent rugae, petechiae and friability of the vaginal wall constituted the atrophic domain of the vaginal examination. These physical characteristics were statistically significantly associated with two biological indices of atrophy: low maturation index and high vaginal pH. A separate physical examination domain, inflammation, was described by redness of the labia minora, redness of the vaginal walls and a red urethral meatus/caruncle. This domain was not correlated, however, with cytological smear readings of inflammation. Symptoms of dryness and itching/irritation were poorly correlated with either atrophy or inflammation.

Previous methods for assessing vaginal atrophy have largely been based on face validity[3,4]. Items believed to represent atrophy have been based on clinical judgement. To the present authors' knowledge, a comprehensive study of criterion validity, to assess whether these physical characteristics do indeed measure atrophy, has not been undertaken. This investigation compiled several examination items believed to represent atrophy on the vaginal examination and assessed their associations with a cytological criterion for atrophy, the maturation index, and a physiological criterion, pH[9]. The observed correlations between the atrophy physical examination subscale and the biomarkers of atrophy support the hypothesis that conization, absence of rugae, petechiae and friability of the vaginal wall are indeed physical findings of vaginal atrophy. These results offer objective validation that the physical characteristics of atrophy proposed here and by others[3–5] are a valid clinical description of this condition.

It was also proposed that physical signs of inflamma ion represented a different domain from that represented by atrophic signs, and this hypothesis was, in part, supported by the above findings. The proposed inflammation characteristics of the vaginal examination were not correlated with the biomarkers of atrophy, suggesting that these examination items were assessing features distinct from atrophy. However, the proposed atrophy examination findings and those believed to represent inflammation were moderately correlated with each other. Additionally, a relationship was not found between the inflammation subscale

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and a vaginal smear reading of inflammation; thus, this measure of criterion validity was not upheld. One possible explanation for the lack of association, however, is that the cytological smear inflammation reading was not specific for vaginal inflammation. The cytopathological criteria for inflammation allowed a positive reading if either cervical or vaginal tissues were involved.

The atrophy and inflammation subscales were reliable, with high degrees of inter-rater agreement for each of the six items tested. To the present authors' knowledge, this is the first evaluation of inter-rater agreement for a clinical vaginal examination. In part, high agreement was accomplished by the use of binary (i.e. characteristic present vs. absent) response categories. While binary response categories promote reproducibility, they are likely to obscure finer gradations in the spectrum of the atrophic or inflammatory process. However, since it was not possible to accomplish an acceptable degree of agreement between raters when a three-level response was used in phase I, reproducibility was opted for rather than more finely graded scoring. However, using the binary response set, the scale may prove to be suboptimal for assessing change in the vaginal examination. Studies using this scale to detect change in response to therapy are under way.

The symptoms of itching/irritation or dryness, present in a quarter to a half of participants, were often not present when physical signs proposed to represent atrophy or inflammation were found. The relatively poor agreement between examination findings and clinical complaints corroborates previous work[2,10] and highlights an important question: how should the clinical condition 'atrophic vaginitis' be operationalized? One method of defining the condition would be to use a symptom-based criterion (i.e. the presence of vaginal symptoms, in the absence of other causes such as vaginal infection, constitutes 'atrophic vaginitis'). If this approach is taken, the present data imply that physical examination findings of atrophy are moderately sensitive (78%) for diagnosis of 'atrophic vaginitis' but that examination findings of inflammation are very insensitive (43%). While some authors have recommended treatment of asymptomatic physical findings of atrophy to 'prevent progression'[11], outcome-based evidence that preventive intervention is necessary in asymptomatic women is lacking. If symptoms are used to define the presence of atrophic vaginitis, the present study suggests that the majority of women with examination-based atrophic findings would not require therapy.

Limitations of the present study must be acknowledged. Owing to sample size considerations, two items describing cervical anatomy were omitted that did correlate highly with the remaining atrophy items. Future studies will test the performance of the atrophy subscale with the cervical items included. Also, the list of possible symptoms of vaginal atrophy and inflammation was not extensive, and in further studies this list will be expanded to include additional items discharge, dyspareunia, etc.) Additionally, a broader response set (for example, a Likert-type rating scale) may enhance the ability to detect symptoms and may improve the relationship between self-reported symptoms and physical examination and biological parameters. Lack of correlations may also have arisen from the small sample size and therefore limited statistical power. However, this would primarily affect the statistical tests of association and not the estimated effect size. For those circumstances where no association was found, the point estimates of the correlations were quite low. Finally, the phase II sample was limited to breast cancer survivors, whose results may not be generalizable to all postmenopausal women.

In summary, a reproducible and validated four-item scale for the assessment of vaginal atrophy is presented. Also, the existence is proposed of a distinct domain, inflammation, characterized by redness of the labia, vaginal walls and urethra. However, it was not possible to show criterion validity for this three-item inflammation subscale. Further studies to assess longitudinal behavior of examination findings in relation to an expanded list of symptoms, and the response of symptoms and examination findings to interventions, will help to clarify the appropriate clinical definition of 'atrophic vaginitis' and the responsiveness of this scale to change.

Conflict of interest Nil.

Source of funding This work was supported by the following grants: DAMD 17–04–J–4507; National Institute on Aging (NIA) (AG10415–08); Iris Cantor–UCLA Women's Center and the UCLA Center of Excellence in Women's Health (PHS 282–97–0025) (GAG); and a MERIT award from the NIA (JGO).

is this the correct word to use here? do you mean 'defined'?

'DAMD' in full? & defn.

'NIA' correct?

expressed correctly, ie. joint Iris Cantor and UCLA Women's Center?

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APPENDIX

Item	*Definition*
Proposed atrophy indicators	
Petechiae on vaginal walls (present/absent)	petechiae are defined as non-blanching, sub-epithelial hemorrhages that appear as small dark red or purplish spots
Vaginal wall friable (present/absent)	vaginal wall is considered friable if any bleeding occurs during examination (e.g. when speculum is opened or when cotton tip applicator is applied)
Conization (present/absent)	conization is defined as present if speculum cannot be opened once inserted
Rugae (present/absent)	rugae are defined as folds in lateral vaginal walls: if *any* folds are present, at least on one side, then rugae are present; if walls are entirely smooth (flat), folds are absent; this assessment is performed by examining lateral walls with speculum blades open
Cervix flattened (present/absent)	cervix is defined as flattened if, by palpation, it is estimated at less than 1.5 cm in height
Cervix narrowed (present/absent)	cervix is defined as narrowed if, by visual inspection, it is less than full width of posterior vaginal vault
Proposed inflammation indicators	
Labia minora red (present/absent)	any amount of bright red coloration, anywhere on labia minora, defines this condition as being present
Urethral meatus red (present/absent)	urethral meatus is defined as red when there is any amount of redness on meatus, in absence of urethral caruncle or prolapse (cannot be scored if caruncle present)
Bright red areas on vaginal walls (present/absent)	bright redness is defined when 'beefy' redness, which may be diffuse or patchy, is present in at least one area on vaginal walls
Red urethral caruncle (present/absent)	caruncle is defined as presence of polypoid mass in area of urethral meatus: its color is described as bright red (abnormal) or dark red (wine colored, normal) (if caruncle present, do not score urethral meatus color)

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APPENDIX 3

MENOPAUSE AND BREAST CANCER: SYMPTOMS, LATE EFFECTS AND THEIR MANAGEMENT

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Acknowledgments: Dr. Ganz is supported by research funding from the National Cancer Institute R01 CA 63028, the Susan G. Komen Foundation, and the Department of Defense DAMD 17-94-J-4507 and 17-98-1-8180. The author thanks Gerald Hitsman for preparation of figures 1 and 2.

Abstract

The menopause and breast cancer are common independent health events, and coincide in some women. This article will describe what is known about the impact of menopause on breast cancer survivors focusing on short-term symptoms and other late effects. Common menopausal syndromes in breast cancer survivors will be examined, with suggestions for their management. Strategies for prevention of the late effects of menopause in breast cancer survivors will be considered.

Introduction

Like puberty, menopause is a life transition that all women will experience. Historically, discussion of the menopause in public (or even within the provider-patient relationship) has been quite limited. Several publications in the lay press have broken this taboo recently (1-3), and it is clear that what was once a forbidden topic is now a pressing issue for many women. With the baby boomers passing into this phase of life, interest in the menopause as a women's health issue has increased. Research efforts such as the Women's Health Initiative, a study of several health and lifestyle interventions for women over 50 years, have attracted the attention of both the scientific and lay communities.

Given this contextual background, it is not surprising that women with breast cancer are equally concerned about this aspect of their health. What is the relationship between menopause and breast cancer? How do these two life events interact with each other? How does each event affect the health and quality of life of breast cancer survivors? Although breast cancer is a common disease and menopause is a universal event, relatively little is known about the effects of each condition on the other. This article will describe what is known about the impact of menopause on breast cancer survivors, focusing on short-term symptoms and other late effects. Common menopausal syndromes in breast cancer survivors will be examined, with suggestions for their management. Strategies for prevention of the late effects of menopause in breast cancer survivors will be considered.

Menopause

Menopause is clinically diagnosed when a previously menstruating woman with an intact uterus has amenorrhea for at least 12 months. The average age of menopause in North American women is 51 years (4). There are secondary forms of amenorrhea that may be related to

endocrine disorders or conditions such as anorexia nervosa; however, women with these conditions are not considered menopausal unless the conditions are irreversible. Causes of secondary amenorrhea are not considered in this discussion, with the exception of cancer treatment induced amenorrhea.

Other useful terms to define include *premenopausal*- a woman who was menstruating regularly (cycle length 24-35 days) during the past 12 months; *perimenopausal* - a woman who has menstruated during the past 12 months, but is experiencing changes in her menstrual cycle length and menstrual irregularity (cycle length greater than 6 weeks), as well as occasional symptoms associated with estrogen deficiency (hot flashes, palpitations, sweats, vaginal dryness, urinary incontinence, sleep disturbance); *postmenopausal* - a woman with an intact uterus who has not had a menstrual period in over 12 months, and who may or may not be experiencing symptoms of estrogen deficiency **(see figure 1 for a timeline of these phases of reproductive life)**. *Premature menopause* is usually defined as menopause that occurs before age 40. Gynecological surgery (hysterectomy) can complicate the evaluation of woman's menopausal status, as menstrual bleeding can no longer be used to classify her status. If a woman's ovaries are removed as a result of surgery, she will experience a surgically induced menopause.

There is some controversy over whether the menopausal transition is initiated through primary ovarian failure, or through hypothalamic-pituitary changes (5). Nevertheless, the menopausal transition is characterized by a decreased responsiveness of the ovaries to luteinizing and follicular stimulating hormones (LH and FSH). A subtle rise in FSH may be one of the earliest hormonal signs of the menopause. Gradually, over time, the estradiol levels fall as the ovarian follicles are depleted and there is no further response to the pituitary gonadotropins LH and FSH. It is with these changes that the clinical symptoms of estrogen deficiency begin to

occur. Lowered levels of estradiol affect various target tissues including the vagina, the skin, the bone, vascular endothelium and smooth muscle, as well as the hypothalamic temperature regulating centers. The ovaries are the primary source of androgens in women, even into the postmenopause, and decreased production of ovarian androgens may account for changes in libido during this time. The responses to decreased ovarian hormones in individual women are not predictable, as other sources of estrogen (e.g., production of estrogen by conversion of adrenal androgens to estrogens in peripheral fat tissue) may limit the symptoms of ovarian estrogen deficiency. Therefore, obese postmenopausal women are often protected from estrogen deficiency symptoms and other health related problems (e.g., osteoporosis).

There have been several epidemiological research studies that have examined the effects of the development of menopause on women's health (6-8). Some have focused on the psychological health and well being of these women, and others have examined physiological changes. Overall, these studies suggest that most women adapt well as they experience the menopause, without an excess of depression or other psychological symptoms. However, many women who become menopausal experience several symptoms associated with estrogen deficiency, and these include vasomotor symptoms (hot flashes, sweats, palpitations), urinary incontinence, and vaginal dryness. Vasomotor symptoms are most frequent (up to 75% of menopausal women experience these at some point in time) and are among the earliest symptoms of the menopause, with urinary incontinence and vaginal dryness increasing slowly during the later postmenopausal years. While the data from these epidemiological studies are of value as a starting point, they are limited by cross-sectional design in some cases, as well as limited ethnic diversity. An ongoing prospective cohort study of women transitioning from the perimenopause to menopause (the Study of Women Across the Nation [SWAN]), will be one of the first studies

to examine comprehensively the physiological, psychological and quality of life aspects of menopause, in a nationally representative multi-ethnic sample of women.

In addition to the symptoms associated with menopause, there may be other long-term effects from the changes in estrogen levels during the menopausal transition. Cholesterol levels gradually rise in postmenopausal women, and over the decade following menopause the risk of atherosclerotic heart disease increases substantially. Estrogen also plays an important role in vasomotor tone and vascular wall cholesterol uptake and metabolism. Thus, declining levels of estrogen in the postmenopause are associated with an increased risk of atherosclerotic cardiovascular disease (9). In addition, the salutary effects of estrogen on bone mineral metabolism are well known, and the decline in estrogen during the perimenopausal transition can accelerate the normal age-related decline in bone density. For these reasons, estrogen replacement therapy has been widely advocated at the time of the menopause for the amelioration of these potential health problems (10, 11)

While the hormonal changes associated with menopause are universal, the symptoms and psychosocial correlates of menopause are not, as demonstrated in cross-cultural comparisons (12). To some extent, in North America this natural transition has been medicalized to be a "hormone deficiency state" requiring treatment. In other societies, such as Japan, hormone replacement therapy is rare and women have long and productive lives without medical intervention. The emphasis on the use of hormone replacement therapy (HRT) in North America sets up an enormous tension for health-conscious breast cancer survivors who often feel deprived of what the medical profession is widely prescribing to women without a history of breast cancer. The safety and efficacy of HRT is only now being tested in a first randomized trial (the Women's Health Initiative) that will be large enough to determine whether there are substantial

preventive benefits for cardiac, bone and cognitive outcomes in healthy aging women. In addition, cancer outcomes such as the prevention of colorectal cancer and risk of breast cancer will be assessed. Although the benefits of HRT in the management of clinical osteoporosis have been tested in efficacy studies, other alternatives to HRT are available (13). There is still substantial controversy about the cardiovascular prevention benefits of HRT. In the recently published Heart and Estrogen/progestin Replacement Study (HERS) trial (14), a randomized, placebo controlled trial of HRT in women at high risk for cardiac events, the investigators found no significant benefit of therapy in women with serious coronary artery disease. In addition, the thromboembolic event rates from HRT in the HERS trial were comparable to therapy with tamoxifen (15). A recent authoritative review on the subject of HRT and heart disease suggests that "until findings from randomized trials confirm and quantitate the benefit of estrogen therapy for prevention of coronary heart disease, ...it should not be recommended to all postmenopausal women (9)."

Finally, there is increasing evidence for a more heterogeneous view of the postmenopausal population of women (See figure 2). Endogenous levels of estrogen play an important protective role in the development of osteoporosis over a woman's lifetime. Postmenopausal estrogen levels (principally estrone) are related to body mass index, and the extent of body fat. Leaner postmenopausal women tend to have more vasomotor symptoms and a greater risk of osteoporosis. Two large cohort studies have now shown that women at risk for osteoporotic fractures in the postmenopause are at a substantially reduced risk of developing breast cancer (16, 17), and this has been supported by data on circulating levels of estrogen in these postmenopausal women (18). In contrast then, women who develop breast cancer as a group are likely to have had greater life time exposure to endogenous estrogen (19) and as a

group are likely to have a lower risk of osteoporotic fracture. For heart disease, we do not have similar epidemiological data; however, if endogenous estrogen turns out to be protective in the postmenopause, then many breast cancer patients may not need to fear this late effect of menopause as well.

Relationship of Estrogen Levels and Menopause to Breast Cancer

In Western industrialized countries, breast cancer is the most common cancer in women, primarily affecting women in the postmenopausal years. In the US, approximately 75% of all new cases of breast cancer occur in women 50 years of age and older. While there is a small rise in breast cancer incidence at or around the time of the menopause, the disease has a bimodal incidence pattern with a much larger peak incidence in elderly women in the eighth decade of life (i.e., about 20 to 30 years after the menopause). This late onset, postmenopausal peak is most common in Western industrialized countries, where ecological studies show a high correlation with intake of dietary fat (20). The breast cancer/dietary fat controversy is an active one, and the effect of a low fat dietary intervention program in preventing breast cancer in postmenopausal women is being tested in the Women's Health Initiative.

The risk of breast cancer is also associated with lifetime weight gain, as well as obesity in postmenopausal women (20, 21). Thus, a more plausible explanation for the increased incidence of breast cancer in postmenopausal women is the sustained level of endogenous estrogen from increased body fat and the peripheral conversion of androgens to estrogens (19). In lean postmenopausal women who do not take hormone replacement therapy (HRT), estradiol levels fall to nearly pre-pubertal levels. Epidemiological studies support the hypothesis that endogenous hormone levels and reproductive history are strongly related to breast cancer risk, primarily through estrogen's growth promotion of normal and neoplastically transformed breast

cells (19). Oophorectomy in premenopausal women protects against a subsequent risk of breast cancer, and early menarche and late menopause increase the risk of breast cancer (19). The role of postmenopausal HRT in breast cancer pathogenesis is controversial, with observational studies and meta-analyses showing evidence for a small increased risk in postmenopausal women with more than a decade of exposure (19, 22). The Nurses Health Study recently reported data suggesting that after 5 years of combined estrogen/progestin therapy, current users over age 60 were at a 40% increased risk of breast cancer, although the risk diminished in former users (23). Their report suggests that short-term use of HRT for symptom management may not increase substantially the risk of breast cancer in postmenopausal women. There are many potential biases in these non-randomized, observational studies of HRT use and breast cancer risk (e.g., healthier women use HRT, women with symptoms and lower endogenous estrogen levels use HRT, women without a family history of breast cancer are more likely to use HRT). Therefore, these studies may underestimate the actual risk of breast cancer after long-term HRT use (19). For the same reasons and biases, they may overestimate the cardiovascular benefits of HRT (9).

Common Menopausal Syndromes in Breast Cancer Survivors

As discussed earlier, breast cancer is primarily a disease of postmenopausal women. For this group of women, the breast cancer may coincide with existing menopausal symptoms such as hot flashes, vaginal dryness, change in mood, and urinary incontinence, or with long-term use of estrogen for its purported preventive benefits. HRT usually is stopped abruptly at the time of the breast cancer diagnosis. As a result, the patient is likely to experience a recurrence of vasomotor symptoms at the same time she is dealing with the shock of her cancer diagnosis. If she requires adjuvant therapy with either tamoxifen or chemotherapy, she may have additional

treatment related side effects to deal with at the same time. Tamoxifen, in particular, may lead to an increase in the frequency and severity of hot flashes (24, 25). Clinically, tamoxifen therapy in postmenopausal women has been associated with both vaginal dryness and increased vaginal secretions. Recent data from the NSABP P-1 Trial comparing tamoxifen to placebo in healthy women at high risk for breast cancer did not demonstrate excess vaginal dryness in the women taking tamoxifen (26). However, women in all age groups on tamoxifen experienced more frequent hot flashes, night sweats, and vaginal discharge than women taking placebo (26).

For the premenopausal breast cancer patient, there are other special considerations. Chemotherapy is the primary form of adjuvant therapy for younger women with breast cancer, and as a result of treatment with the alkylating agent cyclophosphamide, many premenopausal women are at risk of ovarian failure. The latter can occur at any age, but is most common in women older than 40 years and least likely in women less than 30 years (27). Ovarian dysfunction secondary to chemotherapy can be transient or permanent, but many women will stop menstruating within the first few cycles of chemotherapy and then never resume menstruation (see Figure 1). Under these circumstances, they are thrown into menopause abruptly, with symptoms as profound as those associated with surgical castration. Unlike the usual perimenopausal transition that lasts from five to ten years, letting the woman's body gradually adjust to declining estrogen levels, these women suffer severe symptoms from the sudden change in hormone levels. These changes usually come without much warning (unless the health care provider has adequately prepared the woman), and add to the psychological and physical burdens associated with the recent breast cancer diagnosis and surgery. Not only does the younger woman have breast cancer, but she must now face early menopause as well.

Tamoxifen is sometimes used as the sole adjuvant therapy in younger women, and this is generally less troublesome for premenopausal women than for early postmenopausal women. Premenopausal women may experience some irregular menstrual periods from tamoxifen, but in clinical experience hot flashes or vaginal symptoms less frequent. However, data from the recently completed NSABP P-1 trial show that in women age 35-49 years at entry to the trial, the symptoms with the largest relative difference between trial arms between months 3 and 36 months were cold sweats (22.9 % on tamoxifen reported at least once, RR 1.44), vaginal discharge (62.6% on tamoxifen reported at least once, RR 1.35), pain on intercourse (31.6% on tamoxifen reported at least once, RR 1.32), night sweats (74.2% reported on tamoxifen at least once, RR 1.24), and hot flashes (81.3% reported at least once, RR 1.24) (26).

Relatively little information is available on the relationship of menopause and breast cancer to sexual functioning. There is a decline in libido and an increase in vaginal dryness with normal aging (28), and these problems are often exacerbated as a result of breast cancer treatment. Women with breast cancer who develop ovarian failure from chemotherapy or who undergo surgical oophorectomy as treatment for breast cancer, can experience androgen deficiency that can accelerate the normal age-related changes in libido (as discussed earlier). Similarly, the vaginal epithelium may become atrophic from estrogen deprivation (natural or treatment-induced menopause), and this can lead to clinical symptoms of vaginal dryness and dyspareunia. We surveyed a large sample of breast cancer survivors (N=862) who were assessed on average 3 years after their breast cancer diagnosis. We found that sexual functioning in these women was very similar to healthy volunteer women participating in the Postmenopausal Estrogen Progestin Intervention (PEPI) trial (29, 30). However, the breast cancer survivors

reported higher rates of hot flashes and vaginal dryness than age-matched healthy controls (29, 30).

In a second independent sample of breast cancer survivors (N=1096) (31), we examined the impact of adjuvant therapy on quality of life, sexual functioning and menopausal symptoms. The sample was divided into the four following groups according to the type of adjuvant therapy that had been given: no adjuvant therapy (N=265), tamoxifen alone (N=365), chemotherapy alone (N=180) and chemotherapy and tamoxifen (N=395). Age and time since diagnosis were controlled for in all analyses, as these were the only variables that were significantly different among the groups. Sexual functioning scores differed significantly among the groups ($p=0.0078$) with patients receiving chemotherapy (either alone or with tamoxifen) experiencing more problems. Hot flashes, night sweats, and vaginal discharge differed by treatment ($p=0.0001$); all symptoms were reported more often in breast cancer survivors on tamoxifen. Vaginal dryness and pain with intercourse also differed significantly by adjuvant treatment, occurring more often in survivors treated with chemotherapy. Overall, these breast cancer survivors functioned at a high level, similar to healthy women without cancer, in spite of experiencing a significant increase in some menopausal symptoms (31).

In a more complex set of analyses using these two study samples, we developed predictive models for sexual interest, sexual dysfunction and sexual satisfaction among these breast cancer survivors (32). We found that vaginal dryness and past chemotherapy were among the most significant predictors of sexual dysfunction in breast cancer survivors (32). Therefore, strategies for management of vaginal dryness should be tested for women troubled by sexual dysfunction. As for the effects of chemotherapy, a new prospective study being conducted by

the NSABP will examine the impact of different adjuvant therapy regimens, with and without alklyating therapy, on changes in menopausal status, symptoms and quality of life (33).

Managing Menopausal Symptoms in Breast Cancer Survivors

For women without a breast cancer diagnosis, the practitioner's response to most symptoms of menopause is the prescription of hormone replacement therapy (HRT) in one form or another (34). Vaginal atrophy and its associated symptoms are promptly reversed by estrogen. Similarly, increasing the blood levels of estrogen promptly moderates hot flashes, sweats, sleeplessness and other symptoms of vasomotor instability. There may be questions about the most pharmacologically appropriate form of estrogen, but there is little controversy about the effectiveness of this class of hormones in alleviating symptoms. The downside of unopposed estrogen is the risk of endometrial hyperplasia. As a result, any woman with an intact uterus must use some form of progestational agent to counteract this risk. The results of the recently completed PEPI trial shed much light on the benefits and risk (cardiovascular, bone, and uterine endpoints) of several approaches to postmenopausal HRT (35-37).

Where does this leave the breast cancer survivor with uncontrolled menopausal symptoms? Estrogen use has been discouraged systematically in women with a breast cancer history, primarily due to concerns about the risk of metastatic disease recurrence and new primary breast cancers. This stance has been taken by oncologists primarily because of the known role of estrogens as promoters of breast cancer growth both *in vitro* and *in vivo*. Nevertheless, this is also based on a policy of risk minimization rather than evidence-based findings. This policy has recently been called into question in an extensive review of the literature (38,39), as well as some interest at the National Cancer Institute in conducting randomized trials to test the safety and efficacy of HRT in women who have had breast cancer.

An Eastern Cooperative Group trial testing HRT in symptomatic breast cancer survivors who are also taking tamoxifen will soon be launched. What should we do for symptomatic breast cancer survivors until the results of this and other trials are available?

Several groups of investigators have recognized the seriousness of uncontrolled menopausal symptoms in breast cancer survivors, especially those receiving tamoxifen. The North Central Cancer Treatment Group, under the leadership of Dr. Charles Loprinzi, has conducted a series of studies examining non-estrogen alternatives for hot flash control and for treatment of vaginal dryness (see figure 3). The first agent tested for hot flashes was the clonidine patch. Using a double-blind, placebo-controlled, cross-over design (40), in breast cancer survivors on tamoxifen, these investigators found that hot flash frequency and severity could be reduced with this approach, although some side effects made the medication less well-tolerated than the placebo. In a second study (41), using a similar design, symptomatic breast cancer survivors (many on tamoxifen), received megestrol acetate for treatment of hot flashes (low doses ranging from 20 mg to 80 mg/day). This approach was significantly better than placebo and was quite acceptable to patients. While these findings are encouraging, the study used the medication for only a short period of time. In an attempt to evaluate the long-term efficacy of this agent, these investigators subsequently contacted patients who participated in an open label phase of the study (42). They found that 45% of the patients (55% of the men and 31% of the women in the original study) were still taking megestrol acetate approximately 3 years beyond the conclusion of the 1992 study, and the vast majority of these had never stopped the drug. Some had discontinued the medication for a short time but then resumed it when hot flashes returned. More than three-fourths of those persons taking megestrol acetate were using it at a lower dose. Major reasons for discontinuing the medication were no perceived benefit,

gynecological symptoms (vaginal spotting, bleeding, cramping), taking too many other drugs, hot flashes resolved, weight gain or appetite stimulation. These authors concluded that although there is no certainty about whether there are serious risks to long-term megestrol acetate, "many breast cancer survivors are willing to accept this uncertain risk for relief of menopausal symptoms and it does appear quite reasonable to offer this therapy to patients (42)." Other studies performed by the North Central Cancer Treatment Group examined Vitamin E (43) and the antidepressant venlafaxine hydrochloride (44), but as shown in figure 3, these agents have less effect than megestrol acetate on decreasing hot flash scores in symptomatic patients (44).

Vaginal dryness is an equally troubling problem that increases with age in healthy women and may persist long after hot flashes have resolved. One randomized controlled trial comparing estrogen to the vaginal moisturizer Replens has demonstrated improvement in vaginal cytology with this preparation in healthy women (45). The North Central Cancer Treatment Group has tested the efficacy Replens for the management of vaginal dryness and dyspareunia in a placebo controlled trial (46). They found this product to be quite effective in relieving symptoms; however, quite similar results were seen with the placebo (K-Y jelly), which was apparently not an inert substance! In any case, breast cancer survivors need not suffer if practitioners are aware of the results of these studies and if they make therapeutic recommendations for estrogen alternative therapies when these symptoms are reported.

The symptom-control studies conducted by Loprinzi and colleagues are very important, providing careful evidence for the pharmacological efficacy of these non-estrogen alternatives for the relief of these common menopausal symptoms in breast cancer survivors. Nevertheless, these individual trials do not provide guidance about how to integrate these approaches into the clinical management of breast cancer survivors. In an attempt to study these problems in a

clinical setting, we recently completed a randomized, controlled trial testing the value of a comprehensive menopausal management program in breast cancer survivors. A nurse practitioner delivered this clinical intervention to symptomatic breast cancer survivors who were willing to consider a pharmacological intervention for at least one of three target symptoms (hot flashes, vaginal dryness, urinary incontinence). Most of the women were highly symptomatic, with more than 80% having two of the three target symptoms. Using both education, counseling, lifestyle modifications, and several pharmacologic agents (bellergal-S, clonidine patch, megestrol acetate, Replens), after a four month period of intervention we have demonstrated a significant improvement in the target symptoms and sexual functioning in the women assigned to treatment compared to a no treatment control group. Unlike the single agent pharmacological trials, this study tried to address all three symptoms simultaneously, as well as tailor the treatment strategies to the individual woman's needs and her willingness or lack of willingness to take a medication. In this study, we also collected information on hormone levels and vaginal cytology, to obtain a better understanding of the relationship of endocrine physiology to symptoms, and these results should be forthcoming shortly. Our results to date suggest that clinicians can have success in applying existing non-estrogen therapies in managing menopausal symptoms in breast cancer survivors prior to consideration of HRT.

What about alternative or complementary therapies? Many women approached to participate in our randomized trial were reluctant to try medications for treatment of their menopausal symptoms, and in fact those who did participate had very severe symptoms. Most had tried a wide range of herbs, vitamins, and soy products, and were still symptomatic. There is currently much interest in alternative or natural therapies among healthy women and breast cancer survivors (47), and these range from soy protein in powder form, or as food products, to

oil of evening primrose oil, to yam creams (a source of natural progesterone). Few of these substances have been subjected to randomized controlled trials, and given the substantial effect of placebos noted in Loprinzi's studies (see figure 3), some women with mild to moderate symptoms may benefit from these therapies. Physicians should be aware of the widespread use of these remedies and discuss with their patients what they are taking. Many of these substances may mimic the effects of estrogen in the central nervous system, and relieve symptoms and lower FSH. Whether they present a risk for breast cancer recurrence is not known, and some (such as phytoestrogens) are being explored for their potential as preventive agents.

Is it ever safe to use estrogen in breast cancer survivors? This is one of the most controversial questions in clinical practice today, and there are strong feelings on both ends of the spectrum. Many patients have severe impairment in quality of life due to uncontrolled vasomotor symptoms, vaginal dryness or serious mood disturbance, that only estrogen therapy will relieve. Use of estrogen in these women almost always occurs after a trial of non-estrogen approaches (as described above), and in many cases after withdrawal of tamoxifen. Most of these women are many years after their initial breast cancer diagnosis with an excellent long-term survival outlook, and the small risk of recurrence is outweighed by their current distress. For women with vaginal symptoms as the major problem, topical use of vaginal estrogen cream or the estring (48) may make a substantial difference in quality of life and have little effect on systemic estrogen levels. Because of the uncertain risks of HRT in the setting of breast cancer, the woman must be informed about the limitations of our information at this time, and should be encouraged to make a decision that is most consistent with her beliefs and values.

Management of Late Health Consequences of the Menopause in Breast Cancer Survivors

As with any preventive strategy, individuals must perceive themselves to be at risk of the condition in order to obtain adherence to the treatment regimen. In an interview study conducted with breast cancer survivors who were 60 years of age and older (49), we found that they were extraordinarily risk averse and would be unwilling to take HRT for prevention of either heart disease or osteoporosis. About two-thirds of them would, however, consider HRT if they had all three severe and uncontrolled menopausal symptoms (hot flashes, vaginal dryness, urinary incontinence). Most breast cancer survivors, and many healthy women who fear the potential risk of breast cancer from HRT, would rather consider other strategies to reduce their risk of heart disease and osteoporosis. Fortunately, exercise, diet, calcium supplementation, as well as several new agents for cholesterol lowering and osteoporosis treatment, can all be used as alternative approaches to disease prevention and treatment in women who do not wish to consider HRT.

The findings from our study are echoed in the report of a recent consensus conference on "Treatment of Estrogen Deficiency Symptoms in Women Surviving Breast Cancer (50, 51)." This multidisciplinary conference also included breast cancer survivors and advocates. The uncertainties with regard to risks and benefits of estrogen therapy were thoroughly reviewed. In the end, the conference concluded, "In women who have had an established diagnosis of breast cancer, we should seek other established symptomatic or health-promoting interventions before considering the use of estrogens. When estrogen is used as a last resort, it should be used in the lowest dose for the shortest duration of time and only after full discussion of concerns regarding potential risks with respect to breast cancer outcomes. When estrogen is being considered, the

role of the informed woman as the final decision maker should be accepted by the healthcare practitioner (51, p.S5)."

Conclusions

We are living in an exciting time. Survival rates from breast cancer are finally beginning to improve, largely from the more widespread use of screening mammography and the advances in adjuvant therapies. Many women with a breast cancer diagnosis can expect a near normal life span. With these important advances, the quality of life and survivorship concerns of breast cancer patients take on a prominent role. Much more research needs to be done to develop ways to modify the late toxicities of therapy and to manage bothersome symptoms of hormone deficiency. Fortunately, there are a number of ways we can address the management of menopausal symptoms in patients, and hopefully, there will be more effective approaches available in the future.

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Figure Legends

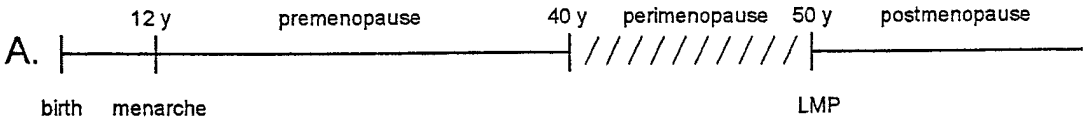
Figure 1. The top part of the figure (A) shows the typical time line for the phases of a woman's reproductive life cycle, with the menopausal transition lasting about 10 years from age 40 to 50 years. Figures B, C, and D show possible scenarios after chemotherapy in a premenopausal woman. For B, chemotherapy is given at age 34 and there is no effect on the perimenopausal transition length or the timing of menopause. For C, chemotherapy is given at age 34 and the perimenopause is shortened by 3 years and menopause occurs about 3 years earlier. For D, chemotherapy is given at age 44 and the woman stops menstruating immediately and experiences menopausal symptoms. LMP=last menstrual period.

Figure 2. Hypothetical distribution of subpopulations of postmenopausal women at risk for various health conditions. Women at low or high risk for breast cancer are shaded in gray. Women at higher risk for breast cancer are generally at low risk for osteoporosis.

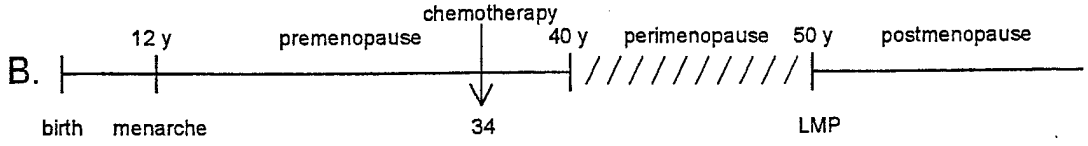
Figure 3. Summary graph of weekly hot flash scores in patients treated on studies conducted by Loprinzi and colleagues, using placebo controlled trials and a phase II trial of venlafaxine. Reprinted with permission from reference Lippincott Williams and Wilkins reference 44.

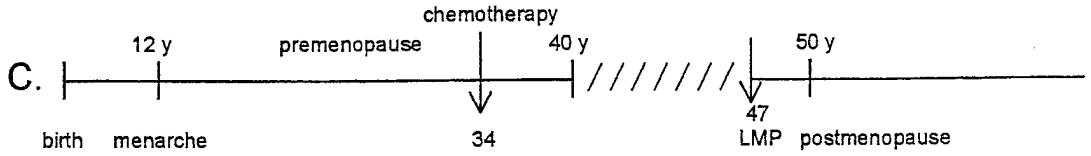
Effect of Adjuvant Chemotherapy on Reproductive Life Cycle

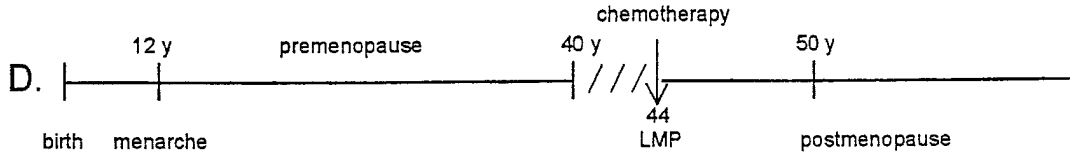
Normal Reproductive Life Cycle



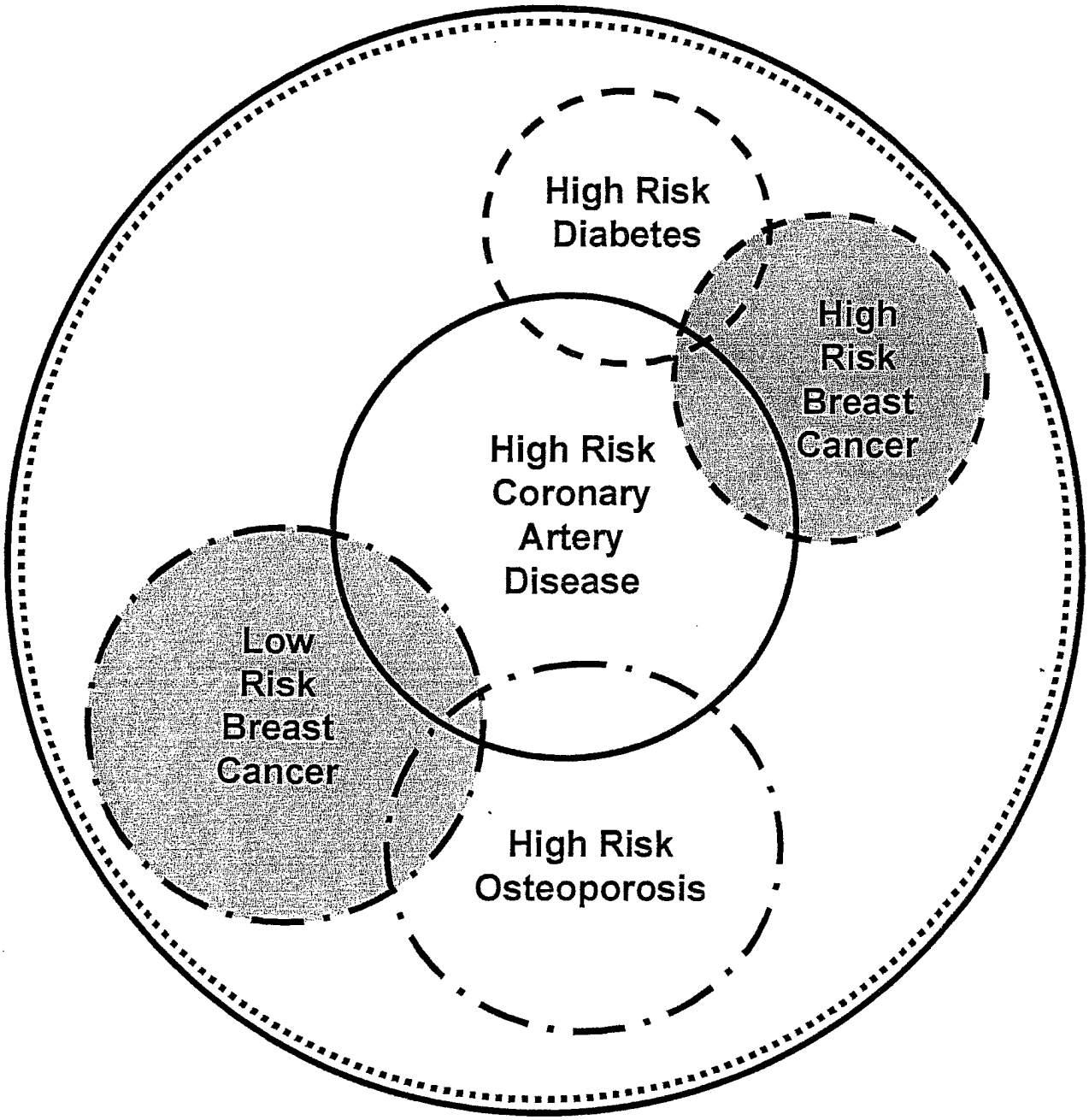
Possible Scenarios After Chemotherapy

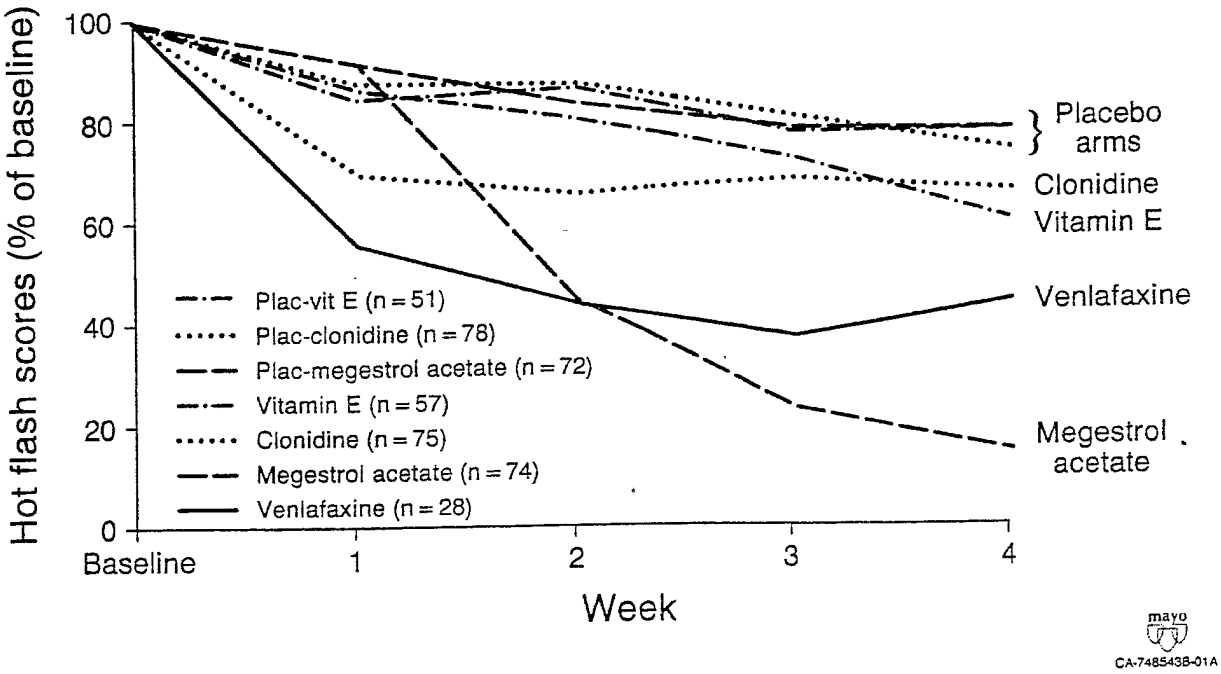






SUBPOPULATIONS OF POSTMENOPAUSAL WOMEN





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